**Appeal No. 2016-1785**

**IN THE**

# United States Court of Appeals

**FOR THE FEDERAL CIRCUIT**

SHIRE DEVELOPMENT, LLC, SHIRE PHARMACEUTICAL DEVELOPMENT, INC., COSMO TECHNOLOGIES LIMITED, and GIULIANI INTERNATIONAL LIMITED,

*Plaintiffs-Appellees,*

v.

WATSON PHARMACEUTICALS, INC. (now known as Actavis, Inc.), WATSON LABORATORIES, INC. – FLORIDA (now known as Actavis Laboratories FL, Inc.), WATSON PHARMA, INC. (now known as Actavis Pharma, Inc.), and WATSON LABORATORIES, INC.,

*Defendants-Appellants.*

Appeal from the United States District Court for the Southern District of Florida in case no. 12-60862-CIV, Judge Donald M. Middlebrooks.

## BRIEF OF DEFENDANTS-APPELLANTS WATSON PHARMACEUTICALS, INC. (now known as Actavis, Inc.), WATSON LABORATORIES, INC. – FLORIDA (now known as Actavis Laboratories FL, Inc., WATSON PHARMA, INC. (now known as Actavis Pharma, Inc.), and WATSON LABORATORIES, INC.

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May 4, 2016

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# CERTIFICATE OF INTEREST

Counsel for Defendants-Appellants Watson Pharmaceuticals, Inc., Watson Laboratories, Inc. – Florida, Watson Pharma, Inc., and Watson Laboratories, Inc. certifies the following:

1. The full name of every party being represented by me is:

   Watson Pharmaceuticals, Inc. (now known as Actavis, Inc.); Watson Laboratories, Inc. – Florida (now known as Actavis Laboratories FL, Inc.); Watson Pharma, Inc. (now known as Actavis Pharma, Inc.); and Watson Laboratories, Inc.

2. The real party in interest represented by me is: Not applicable.

3. All parent corporations and any publicly held companies that own 10 percent or more of the stock of the parties represented by me are as follows:

   Allergan PLC is a publicly traded corporation that owns more than 10% of Actavis, Inc.

   Actavis Laboratories FL, Inc., Actavis Pharma, Inc., and Watson Laboratories, Inc. are all wholly owned subsidiaries of Actavis, Inc.

4. The names of all law firms and the partners or associates that appeared for the party now represented by me in the trial court or agency or are expected to appear in this Court are:

   Law Firm of Maddox Edwards, PLLC: Steven A. Maddox, Jeremy J. Edwards, and Kaveh Saba;

   Law Firm of Knobbe, Martens, Olson & Bear, LLP: Steven A. Maddox, Jonathan E. Bachand, and Neil M. McCarthy;

Law Firm of Crowell & Moring LLP: James K. Stronski, Bruce D. DeRenzi, Neil M. McCarthy, Mark T. Jansen, Keith J. Harrison, Kristin M. Cooklin, Jennifer H. Burdman, and Craig P. Lytle; and

Law Firm of Rosco Klock Perez & Neito, P.L.: Janet T. Munn.

Respectfully submitted,

**MADDOX EDWARDS, PLLC**

Dated: May 4, 2016

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## STATEMENT OF RELATED CASES

An earlier appeal from the United States District Court for the Southern District of Florida, in case no. 12-60862-CIV, was before this Court, *Shire Development, LLC, Shire Pharmaceutical Development, Inc., Cosmo Technologies Limited, and Giuliani International Limited v. Watson Pharmaceuticals, Inc. (now known as Actavis, Inc.), Watson Laboratories, Inc. – Florida (now known as Actavis Laboratories FL, Inc.), Watson Pharma, Inc. (now known as Actavis Pharma, Inc.), and Watson Laboratories, Inc.*, No. 2013-1409. The earlier appeal was heard by a panel composed of Chief Judge Rader and Circuit Judges Prost and Hughes, and initially decided on March 28, 2014. That decision was vacated and remanded by the Supreme Court of the United States for further consideration in light of *Teva Pharmaceuticals, Inc. v. Sandoz, Inc.*, 135 S. Ct. 831 (2015). After remand from the Supreme Court, a panel composed of Chief Judge Prost and Circuit Judges Chen and Hughes re-issued the decision on June 3, 2015. The opinion is published as *Shire Development, LLC v. Watson Pharmaceuticals, Inc.*, 787 F.3d 1359 (Fed. Cir. 2015).

Shire Development, LLC, Shire Pharmaceutical Development, Inc., Cosmo Technologies Limited, and Giuliani International Limited (collectively, "Shire" or "Plaintiffs-Appellees") have asserted U.S. Patent No. 6,773,720 ("the '720 patent") in numerous other actions that are currently pending: *Shire Dev., LLC v. Cadila*

*Healthcare Ltd*., No. 1:10-cv-00581 (D. Del.); *Shire Dev., LLC v. Osmotica Pharm. Corp.*, No. 1:12-cv-00904 (N.D. Ga.); *Shire Dev., LLC v. Mylan Pharm., Inc.*, No. 8:12-cv-01190 (M.D. Fla.); *Shire Dev., LLC v. Lupin Ltd*, No. 8:15-cv-03437 (D. Md.); and *Shire Dev., LLC v. Amneal Pharm. LLC*, No. 1:15-cv-2865 (D.N.J.). Counsel for Defendants-Appellants is not aware of any other cases pending in this or any other court that will directly affect or be directly affected by this Court's decision in this appeal.

## JURISDICTIONAL STATEMENT

The United States District Court for the Southern District of Florida had jurisdiction of this patent infringement case under 28 U.S.C. §§ 1331 and 1338. Following a bench trial, the district court issued an opinion and order on March 28, 2016, finding the asserted patent infringed, and issued a final judgment in favor of Plaintiffs-Appellees. (Appx1–2.) Defendants-Appellants Watson Pharmaceuticals, Inc. (now known as Actavis, Inc.), Watson Laboratories, Inc. – Florida (now known as Actavis Laboratories FL, Inc.), Watson Pharma, Inc. (now known as Actavis Pharma, Inc.), and Watson Laboratories, Inc. timely filed a notice of appeal on March 29, 2016. (Appx2198.) This Court has jurisdiction over this appeal from the final judgment of the district court under 28 U.S.C. §§ 1291 and 1295(a)(1).

## STATEMENT OF THE ISSUES

1. Did the district court err by failing to follow the instructions of this Court's prior June 3, 2015 opinion in construing the "inner lipophilic matrix" and "outer hydrophilic matrix" limitations of the '720 patent to again include the "at least one lipophilic [or hydrophilic] excipient" language and further:

   a. to allow the "inner lipophilic matrix" to exhibit hydrophilic properties, and thus to embrace a structure comprised overwhelmingly (greater than 95%) of hydrophilic excipients and a single lipophilic excipient in an unproven amount of less than 5%;

   b. to find that the "main component" of the "lipophilic matrix" means any amount of a single lipophilic excipient; and

   c. to mean that two volumes with shared lipophilic and hydrophilic excipients throughout nevertheless can constitute separate lipophilic and hydrophilic matrices?

2. As a result of its erroneous claim constructions, did the district court clearly err when it found that the four hydrophilic substances within the "inner lipophilic matrix" did not violate the "consisting of" transitional phrase that limits the composition of the "inner lipophilic matrix" to a *Markush* group confined to certain lipophilic substances, especially in light of this Court's prior June 3, 2015 opinion?

3. As a result of its erroneous claim constructions, did the district court clearly err when it found that the lipophilic substance within the "outer lipophilic matrix" did not violate the limiting "consisting of" *Markush* group confined to certain hydrophilic substances, especially in light of this Court's prior June 3, 2015 opinion?

## STATEMENT OF THE CASE

This case arose under the Hatch-Waxman Act, based on Watson Laboratories, Inc. – Florida's filing of Abbreviated New Drug Application ("ANDA") No. 203817 and its certification that its proposed ANDA product would not infringe any claim of U.S. Patent No. 6,773,720 ("the '720 patent"). (Appx4–5.) Plaintiffs-Appellees Shire Development, LLC, Shire Pharmaceutical Development, Inc., Cosmo Technologies Limited, and Giuliani International Limited (collectively, "Shire" or "Plaintiffs-Appellees") brought suit against Defendants-Appellants Watson Pharmaceuticals, Inc. (now known as Actavis, Inc.), Watson Laboratories, Inc. – Florida (now known as Actavis Laboratories FL, Inc.), Watson Pharma, Inc. (now known as Actavis Pharma, Inc.), and Watson Laboratories, Inc. (collectively, "Watson" or "Defendants-Appellants") seeking declaratory relief and an order prohibiting the approval of the generic pharmaceutical product described in ANDA No. 203817 ("Watson's ANDA product") until after expiration of the '720 patent. (Appx5–7.)

The district court held a first bench trial on April 8, 2013 through April 12, 2013, and issued an opinion on May 9, 2013, finding claims 1 and 3 of the '720 patent ("the asserted claims") infringed and not invalid. (Appx7.) Watson timely appealed. (Appx7.) On June 3, 2015, this Court reversed and remanded for proceedings consistent with its opinion. (Appx8.) *Shire Dev. LLC v. Watson*

*Pharm., Inc.*, 787 F.3d 1359, 1368 (Fed. Cir. 2015). The district court held another bench trial on remand on January 25, 2016 through January 27, 2016, with closing arguments held on March 23, 2016. (Appx3–4.) The district court entered an order and opinion on March 28, 2016, again finding that Watson's ANDA product would infringe the asserted claims of the '720 patent. (Appx34.) This order and the district court's reasoning for entering it are in direct contravention of this Court's previous opinion.

## A. The Asserted Patent and Claims

The two asserted claims of the '720 patent are claims 1 and 3, reproduced below with the "inner lipophilic matrix" and "outer hydrophilic matrix" limitations emphasized, including their respective "consisting of" restrictions.

> Claim 1:
>
> Controlled-release oral pharmaceutical compositions containing as an active ingredient 5-amino-salicylic acid, comprising:
>
> > a) an **inner lipophilic matrix consisting of substances selected from the group consisting of** unsaturated and/or hydrogenated fatty acid, salts, esters or amides thereof, fatty acid mono-, di- or triglycerids, waxes, ceramides, and cholesterol derivatives with melting points below 90° C., and wherein the active ingredient is dispersed both in said the lipophilic matrix and in the hydrophilic matrix;
> >
> > b) an **outer hydrophilic matrix** wherein the lipophilic matrix is dispersed, and said outer hydrophilic matrix **consists of compounds selected from the group consisting of** polymers or copolymers of acrylic or methacrylic acid, alkylvinyl polymers, hydroxyalkyl celluloses, carboxyalkyl celluloses,

> polysaccharides, dextrins, pectins, starches and derivatives, alginic acid, and natural or synthetic gums;
>
> c) optionally other excipients;
>
> wherein the active ingredient is present in an amount of 80 to 95% by weight of the total composition, and wherein the active ingredient is dispersed both in the lipophilic matrix and in the hydrophilic matrix.

Claim 3:

> Compositions as claimed in claim 1, in the form of tablets, capsules, min[i]tablets.

(Appx39 at 6:7–36 (emphases added).)

The specification teaches how to make the multi-matrix composition of the '720 patent. As this Court explained after the first appeal in this case, the "inner lipophilic matrix" of the invention is made by dispersing the active ingredient throughout the melted continuous phase of lipophilic wax. *Shire Dev. LLC v. Watson Pharm., Inc.*, 787 F.3d 1359, 1362 (Fed. Cir. 2015). Once cooled, this forms an ordinary "lipophilic matrix," which is then milled or broken down into discrete lipophilic granules, called "inert matrix granules." *Id.* (Appx37 at 2:50–59, Appx38 at 4:10–16.)

Indeed, the specification explains that using an "inert matrix"[1] was a "known technique" to prepare "sustained, controlled, delayed or anyhow modified release"

[1] It is undisputed that "inert matrix" is a synonym for "lipophilic matrix." (*See, e.g.*, Appx1168 at 115:15–17.)

formulations. (Appx37 at 1:14–16.) The patent describes the "inert matrix" as one "in which the main component of the matrix structure opposes some resistance to the penetration of solvent due to the poor affinity towards aqueous fluids." (Appx37 at 1:17–20.) All five examples follow the specification's teaching, recognized by this Court, of dispersing the active ingredient in low melting lipophilic excipients (*e.g.*, carnauba or bees wax) to form a lipophilic matrix that is broken down into matrix granules. (Appx37 at 2:50–56; Appx38–39 at 4:10–5:45.)

The specification likewise discloses that using a "hydrophilic matrix" was a "known technique" in which "the main component of the matrix structure" opposes progress of the solvent due to "remarkably increase[d] viscosity inside the hydrated layer." (Appx37 at 1:21–26.) The specification explains that "when the tablet is contacted with biological fluids, a high viscosity swollen layer is formed, which coordinates the solvent molecules and acts as a barrier to penetration of the aqueous fluid itself inside the new structure." (Appx37 at 2:60–64.) "In fact, the immediate penetration of water inside the superficial layer of the hydrophilic matrix and the consequent swelling due to the distension of the polymeric chains of the hydrogels, gives rise to a high viscosity hydrated front . . . until the further penetration of water would cause the disintegration of the hydrophilic layer and therefore the release of the . . . lipophilic granules . . . ." (Appx38 at 3:57–4:5.)

The claims further limit the ordinary "inner lipophilic matrix" and "outer hydrophilic matrix" by *Markush* groups, as this Court described in its 2015 opinion. *Shire*, 787 F.3d at 1367 ("The compositions of the inner volume and outer volume, *i.e.*, inner matrix and outer matrix, respectively, are further limited by the *Markush* groups.") These *Markush* groups restrict the claims solely to an "inner lipophilic matrix" that "consist[s] of substances selected from the group consisting of" a specified list of undisputedly *lipophilic* substances, and an "outer hydrophilic matrix" that "consists of compounds selected from the group consisting of" a specified list of undisputedly *hydrophilic* substances. *Id.*[2]

**B. The District Court's 2013 Claim Construction Ruling and Trial Opinion**

Prior to the first appeal in this case, the district court adopted Shire's constructions of "inner lipophilic matrix" and "outer hydrophilic matrix," in a January 16, 2013 claim construction order. (Appx2189–90.) The district court concluded that the term "lipophilic matrix" meant any "macroscopically

[2] The *Markush* group limitations arose by amendment to overcome a prior-art-based rejection of the claims during prosecution. *Shire*, 787 F.3d at 1363 ("The applicants also amended their claims to state that the active ingredient is dispersed in the lipophilic matrix and added a *Markush* group for both the inner lipophilic matrix and the outer hydrophilic matrix."). The claims initially recited "an inner lipophilic matrix consisting of substances with a melting point below 90 degrees [Celsius]." (Appx1891.) The examiner rejected these claims over the prior art. (Appx2058–61.) In response, the applicants added *Markush* groups dictating what substances can and cannot be present in the volumes deemed the "inner lipophilic matrix" and "outer hydrophilic matrix." (Appx2089.)

homogeneous structure in all its volume" that includes "at least one lipophilic excipient, where the matrix is located within one or more other substances." (Appx2155–56; Appx2165; Appx2187–90.) It likewise construed "hydrophilic matrix" to mean any "macroscopically homogeneous structure in all its volume" having "at least one hydrophilic excipient, where the matrix is located outside the inner lipophilic matrix." (Appx2155–56; Appx2165; Appx2172.) The parties stipulated that "hydrophilic" means "having an affinity to water" and that "lipophilic" means "having a poor affinity towards aqueous fluids." (Appx2155–56; Appx2165; Appx2172.)

Applying Shire's claim constructions, the district court concluded that a single excipient within the granules in Watson's ANDA product—an unknown amount of magnesium stearate that crept into the granule pores during manufacturing—was the "inner lipophilic matrix." (Appx2165–2169.) It also determined that a single excipient (sodium starch glycolate) within the extragranular volume was the "outer hydrophilic matrix." (Appx2172–74.) The district court adopted Shire's legal argument that all the other excipients within the granules and the extragranular volume should be ignored as "unrelated" in assessing the additional "consisting of" *Markush* group limitations in the claims. (Appx2168 n.25.)

### C. This Court's Opinion Reversing and Remanding the District Court's 2013 Claim Constructions and Infringement Determinations

On June 3, 2015,[3] this Court reversed the district court's 2013 constructions of "inner lipophilic matrix" and "outer hydrophilic matrix" and the "subsequent infringement determination," and remanded for "proceedings consistent with [the June 3, 2015] opinion." *Shire*, 787 F.3d at 1368. This Court found that the district court's approach produced constructions that "do not reflect the ordinary and customary meaning of the claim terms in light of the intrinsic evidence and are impermissibly broad." *Id.* at 1365. This Court also provided the proper claim construction requirements to be applied on remand.

The Court first observed that the term "inner lipophilic matrix" on its face requires that "the matrix—not just an excipient within the matrix—must exhibit the stipulated-to lipophilic characteristics." *Shire*, 787 F.3d at 1365. It recognized "poor affinity to aqueous fluids" to be the stipulated construction of "lipophilic," and confirmed that a "matrix" is "a macroscopically homogeneous structure in all its volume." *Id.* at 1365. Thus, the macroscopically homogenous structure in all its volume itself, not merely a single excipient within that structure, must be lipophilic—that is, the matrix itself must exhibit poor affinity to water. According

[3] After the Supreme Court vacated this Court's March 28, 2014 opinion and remanded for further consideration in light of *Teva Pharmaceuticals USA, Inc. v. Sandoz, Inc.*, 135 S. Ct. 831 (2015), this Court re-issued its opinion on June 3, 2015. *Shire*, 787 F.3d at 1361.

to the patent specification and this Court's opinion, "this occurs when 'the main component of the matrix structure' is lipophilic." *Shire*, 787 F.3d at 1365–66 (citing Appx37 at 1:17–18).

As this Court further made clear, the correct construction requires that "the matrix that is deemed the 'lipophilic' matrix cannot have hydrophilic properties." *Shire*, 787 F.3d at 1367. Indeed, the "matrices are defined by . . . mutually exclusive compositional characteristics—one hydrophilic, one lipophilic." *Id.* at 1366.[4] The district court's 2013 construction of "lipophilic matrix," however, would improperly encompass a matrix structure containing mostly hydrophilic substances capable of exhibiting hydrophilic properties, as this Court explained:

> Thus, the matrix that is deemed the "lipophilic" matrix cannot have hydrophilic properties. But, a matrix comprised of only one lipophilic substance and several hydrophilic substances—and thus capable of exhibiting hydrophilic properties—would meet the district court's construction of "lipophilic matrix." Such a result contradicts the customary and ordinary meaning of "lipophilic" and "hydrophilic."

*Id.* at 1367.

This Court also held that the correct claim construction "requires that the inner lipophilic matrix must be separate from the outer hydrophilic matrix." *Shire*,

[4] This Court additionally recognized the dichotomy of lipophilicity versus hydrophilicity in noting that "a lipophilic substance has an affinity for lipids and a hydrophilic substance has an affinity for water." *Shire*, 787 F.3d at 1362 n.1.

787 F.3d at 1366. This excludes from infringement a "single mixed matrix with both hydrophilic and lipophilic components." *Id.* at 1367. Whereas the district court's 2013 constructions permitted an arbitrarily selected volume having both hydrophilic and lipophilic excipients to meet the claim limitations, the claims define the matrices by "mutually exclusive spatial characteristics" and "mutually exclusive compositional characteristics." *Shire*, 787 F.3d at 1366.

Finally, the Court confirmed that mutually exclusive lipophilic and hydrophilic *Markush* groups further limit the compositions of the claimed "inner lipophilic matrix" and "outer hydrophilic matrix" to certain lipophilic and hydrophilic substances, respectively:

> The compositions of the inner volume and outer volume, *i.e.*, inner matrix and outer matrix, respectively, are further limited by the *Markush* groups. . . . Accordingly, the correct construction requires that the inner volume contain substances from the group described for the lipophilic matrix (which are all lipophilic substances), and that the outer volume separately contain substances from the group described for the outer hydrophilic matrix (which are all hydrophilic).

*Shire*, 787 F.3d at 1367.

The Court contemplated only one possibility of infringement in which the lipophilic matrix structure contained any hydrophilic excipients. The Court opined that infringement might be possible where "trace of hydrophilic molecules" are

present in an inner matrix volume (which is otherwise entirely lipophilic) as an inherent result of the manufacturing process:

> Whether or not a composition infringes when there is a trace of hydrophilic molecules in the inner volume because of the mixing step inherent in the manufacturing process, for example, is a question for the fact finder. That this question may need to be resolved does not compel a claim construction that departs from the customary and ordinary meaning of the claims, *i.e.*, that the matrices must be "separate" such that they retain their claimed properties and are consistent with their respective *Markush* group limitations.

*Shire*, 787 F.3d at 1368.

**D. Watson's ANDA Product**

Watson's ANDA product is a tablet that contains 1.2 grams of mesalamine as the active pharmaceutical ingredient, and is made by compressing a mixture of hydrophilic mesalamine granules and extragranular excipients.[5] (Appx20; Appx2160–62; Appx2209; Appx2287–89.) None of the relevant facts about the composition and distribution of ingredients within Watson's ANDA product, or its manufacturing process, is in dispute.

To make Watson's granules, the mesalamine API is mixed with 48 milligrams ("mg") povidone, 42 mg copovidone, and 40 mg microcrystalline cellulose ("MCC") in ethyl alcohol granulating liquid, which eventually evaporates

[5] "Excipient" refers to the any ingredient in the pharmaceutical product other than the active pharmaceutical ingredient ("API").

away during manufacturing. (Appx20; Appx2160–62; Appx2209; Appx2287–89.) This mixture is sent through a granulation device to produce granules. (*Id.*) The resulting granules consist of mesalamine and three hydrophilic excipients (povidone, copovidone, and MCC). (*Id.*)

After drying and milling, the granules are mixed with 34 mg sodium starch glycolate ("SSG") and 4 mg colloidal silicon dioxide, and then mixed with 7 mg magnesium stearate. (Appx20; Appx2160–62; Appx2209; Appx2287–89.) The magnesium stearate—a conventional tableting lubricant—is the only lipophilic substance in Watson's ANDA product. (Appx2209–11; Appx1335 at 1–5; Appx1369 at 2–15; Appx1372 at 14–Appx1373 at 10; Appx2162.) The mixture of granules and extragranular excipients is subsequently compressed into tablets, over which an enteric coating is applied before packaging. (Appx20; Appx2160–62; Appx2209; Appx2287–89.)

Shire presented evidence, and the district court found after the 2013 trial, that when the ethyl alcohol used in granulation evaporates during the manufacturing process, it leaves pores in the granules. (Appx2161; Appx2167.) Such pores are to be expected in any conventional wet granulation process. (Appx1367 at 5–17.) The district court found that the extragranularly-added magnesium stearate and SSG infiltrate these pores of the granules upon tablet compression. (Appx2161; Appx2166; Appx2173; Appx2341–46.) This

infiltration results in the magnesium stearate and SSG being distributed throughout the tablet core, both inside and outside the granules. (*Id.*) It is unknown, however, how much of the 7 mg magnesium stearate and 34 mg SSG infiltrate the granules during manufacturing. (Appx32; Appx2341–46.)

As a purely theoretical maximum—assuming *arguendo* that all 7 mg magnesium stearate makes it into the pores of the granules, and without factoring in SSG—lipophilic magnesium stearate could make up at most 5% by weight of the excipient volume in the granules. (Appx32; Appx1341 at 1–24.) The other 95%-plus is hydrophilic povidone, copovidone, and MCC, as well as some unknown amount of hydrophilic SSG. (Appx32 ("[T]he remaining excipients in the volume of the granule were hydrophilic substances."); Appx2209.)

Thus, the excipient volume in the granules—which the district court determined to be the claimed "inner lipophilic matrix" on remand—has the following undisputed composition:

| **Excipient** | **Amount (mg)** | **Property** |
|---|---|---|
| Povidone | 48 | Hydrophilic |
| Copovidone | 42 | Hydrophilic |
| MCC | 40 | Hydrophilic |
| SSG | <34 (unknown) | Hydrophilic |
| Magnesium stearate | <7 (unknown) | Lipophilic |

(Appx32; Appx2209; Appx1335 at 1–5.)

The extragranular volume in Watson's ANDA product—which the district court determined to be the claimed "outer hydrophilic matrix" on remand—has the following undisputed composition:

| Excipient | Amount (mg) | Property |
|---|---|---|
| SSG | <34 (unknown) | Hydrophilic |
| Magnesium stearate | <7 (unknown) | Lipophilic |
| Colloidal silicon dioxide | 4 | |

(Appx2162; Appx2209; Appx2341–46.)

### E. The District Court's 2016 Claim Constructions and Infringement Determinations on Remand

On March 28, 2016, after a bench trial on remand and post-trial briefing, the district court issued an order and opinion finding that Watson's ANDA product literally infringes the asserted claims. (*See* Appx3–34.) The district court again adopted Shire's proposed claim constructions of "inner lipophilic matrix" and "outer lipophilic matrix." (Appx11–17.) It found this time that the excipient volume in Watson's granules was the claimed "inner lipophilic matrix," that the space outside the granules (the extragranular volume) was the claimed "outer hydrophilic matrix," and that the compositions of these matrices did not violate the respective *Markush* group limitations. (Appx20–34.)

### 1. Claim Construction of the "Inner Lipophilic Matrix" and "Outer Hydrophilic Matrix"

Below is a side-by-side of the district court's original 2013 constructions and its modified 2016 constructions in accordance with Shire's proposals.

| Term | District Court's 2013 Constructions | District Court's 2016 Constructions |
|---|---|---|
| "inner lipophilic matrix" | "a matrix including at least one lipophilic excipient, where the matrix is located within one or more other substances'" | "a matrix including at least one lipophilic excipient, where the matrix exhibits lipophilic characteristics and is located within, and separate from, the outer hydrophilic matrix" |
| "outer hydrophilic matrix" | "a matrix of at least one hydrophilic excipient, where the matrix is located outside the inner lipophilic matrix" | "a matrix including at least one hydrophilic excipient, where the matrix exhibits hydrophilic characteristics and is located outside of, and separate from, the inner lipophilic matrix" |

(Appx11; Appx17.)

The 2016 constructions still incorporate the reversed 2013 constructions' language of "a matrix including at least one lipophilic [or hydrophilic] excipient, where the matrix is located within [or outside]" the other matrix. (Appx11; Appx17.) They then tack on the general requirements that the matrices themselves "exhibit lipophilic [or hydrophilic] characteristics," and that the two matrices be "separate." (*Id.*) These additions do not save the district court's constructions from the same errors committed in the 2013 constructions—(i) that the

constructions of "inner lipophilic matrix" and "outer hydrophilic matrix" are internally inconsistent with the constructions of "lipophilic" and "hydrophilic", and (ii) that the "at least one . . ." language violates the *Markush* group limitations and turns them into comprising limitations.

The district court's opinion further construed what it meant that the matrix itself "exhibits lipophilic [or hydrophilic] characteristics." (Appx12–16.) While the district court acknowledged this Court's requirement that the lipophilic matrix "cannot have hydrophilic properties," it decided that here, the prescribed "hydrophilic properties" refer to swelling only. (Appx14; Appx26.) This conclusion directly contradicts the controlling ordinary meaning constructions of "hydrophilic" and "lipophilic." (Appx2156; Appx13; Appx17.) The district court cited as support for this new proposition excerpts from the patent specification describing that the hydrogels of the invention's "hydrophilic matrix" form a swollen layer. (Appx12–13.) It ultimately adopted Shire's interpretation that a matrix with "lipophilic characteristics" is any matrix that does not swell upon exposure to water—even if the matrix exhibits an affinity for water by absorbing it and dissolving in it. (Appx14; Appx26.)

That the district court construed "lipophilic matrix" to exclude swelling, but allowed the matrix to possess other "hydrophilic properties," is confirmed in its conclusion that Watson's granules "did not swell—thus, they did not exhibit

hydrophilic properties." (Appx26.) The district court came to this narrow definition of "hydrophilic properties" despite its explicit recognition that the parties' stipulated-to meaning of "hydrophilic" is "having an affinity to water." (Appx13; Appx29.) That is, the district court committed legal error when it departed from the agreed ordinary and customary meaning, and inferred a special, narrower meaning from an example of the specification, effectively adopting a new construction of the term.

The district court also acknowledged this Court's direction that the matrix itself is lipophilic when "the main component of the matrix structure" is lipophilic. (Appx27–28.) However, the district court ignored that direction by re-defining "main component" to be satisfied by the presence of "at least one lipophilic excipient"—that is, precisely, the claim construction which this Court previously rejected. Specifically, the district court re-defined "main component" to be the component "responsible for the lipophilic . . . behavior." (Appx28.) This definition is met by the mere presence—*in any amount*—of a single lipophilic excipient in the alleged matrix. The inclusion of the "at least one . . ." language leads to the exact same errors this Court rejected previously. No hydrophilic excipient ever could be "responsible for" lipophilic behavior. Without legal or even linguistic authority, the district court rejected the ordinary meaning of "main ingredient" to refer to physical presence and amount of excipients within the

relevant volume. (*Id.*) Thus, under the district court's construction, having "at least one lipophilic excipient" in any amount, however minuscule, means that it is the "main component" and the matrix is lipophilic.

As to this Court's requirement that the matrices be "separate," the district court required only two volumes with "different distributions of excipients that result in separate characteristics." (Appx13–14; Appx21–22.) Instead of focusing on the undisputed presence of lipophilic magnesium stearate—and hydrophilic SSG—throughout both the alleged "lipophilic matrix" and "hydrophilic matrix," the district court turned to alleged behavioral differences in *other* excipients. (Appx21–22.) Without citing any authority, the district court concluded that it could disregard the presence in each volume of the same particular lipophilic and hydrophilic excipients at issue, because other excipients outside the granules "overwhelmed" the lipophilic magnesium stearate, at the same time that the magnesium stearate in the granule was not "overwhelmed" by the hydrophilic excipients making up more than 95% of the alleged "lipophilic matrix." (Appx22; Appx33.)

The district court also mischaracterized as an "entirely new construction" evidence that this Court's claim construction describes the kind of structure referred to as a "lipophilic matrix" by Shire's own experts outside the courtroom—in their own texts and work in the field of pharmaceutical formulation. (*See*

Appx16; Appx1373 at 24–Appx1378 at 5; Appx1168 at 9–Appx1172 at 9; Appx1379 at 4–Appx1381 at 16.) The "lipophilic matrix" that Shire's experts use in the field embodies this Court's requirements discussed above (no hydrophilic properties and the main component must be lipophilic), as well as in this Court's description of the invention. (*See* Appx1477 at 16–Appx1479 at 2; Appx1482 at 10–Appx1484 at 25.) As this Court explained:

> The '720 patent teaches a three-step process to arrive at the claimed composition. *Id*. at col. 2 ll. 48–59. First, one or more low melting, lipophilic excipients are mixed with mesalamine during heating. *Id*. at col. 2 ll. 50–53. Second, the mixture is cooled to form the lipophilic matrix and then reduced in size into "matrix granules containing the active ingredient." *Id*. at col. 2 ll. 54–56. Third, the lipophilic matrix granules are mixed together with hydrophilic excipients and compressed to form tablets. *Id*. at col. 2 ll. 50–53, col. 3 ll. 40–45.

*Shire*, 787 F.3d at 1362.

### 2. Infringement Findings as to the Disputed Limitations Including the Respective "Consisting of" Requirements

The district court's 2016 infringement determination identified the volume of the granules in Watson's ANDA product as the "inner lipophilic matrix," and the extragranular volume as the "outer hydrophilic matrix." (Appx21; Appx24; Appx29–31; Appx33.) As described above, the purported "inner lipophilic matrix" consists of MCC, povidone, copovidone, magnesium stearate, and SSG. The

district court's "outer hydrophilic matrix" consists of magnesium stearate, SSG, and colloidal silicon dioxide.

The district court also found that "neither Shire nor Watson presented evidence as to the exact amount of magnesium stearate within the granule," but that "magnesium stearate could not exceed a theoretical maximum of 5%" of the excipient structure found to be the "inner lipophilic matrix." (Appx32.)

Applying its modified claim constructions, the district court held that 1) the volume of the granules exhibited lipophilic characteristics; 2) the extragranular volume exhibited hydrophilic characteristics; 3) the two matrices are separate; and 4) the compositions of the matrix volumes did not violate the respective *Markush* group limitations.

*First*, the district court relied largely on the presence of lipophilic magnesium stearate in the granules—as an incidental result of wet granulation, no less—in concluding that the granule volume exhibits lipophilic characteristics. The district court stated that "the distribution of magnesium stearate in the volume of the granules exerts resistance to the penetration of solvent," based on its previous findings and Shire's experts' testimony. (Appx24.) It also found that Shire's expert Dr. Dehua Yang's report of a relatively faster water penetration rate in the extragranular space, compared to the granules, supported a conclusion that the granule volume is lipophilic. (Appx25.)

The district court chose to ignore the hydrophilic characteristics of the other excipients inside the granule, at Shire's urging, because "those other excipients are not responsible for the lipophilic characteristics observed in the granules." (Appx25.) The district court pointed to prior testing showing that the mixture of povidone, copovidone, and MCC readily dissolved in water (because these substances are all hydrophilic). (Appx25–26.) This logic is completely circular.

Moreover, although four of the five substances, and the overwhelming majority by weight, of the purported "inner lipophilic matrix" are hydrophilic, the district court found that "the granules released from the Watson ANDA Product did not swell—thus, they did not exhibit hydrophilic characteristics—as they would if the [SSG] in the granules had any effect." (Appx26; Appx32.) The district court's opinion did not address evidence from Shire's own experts showing hydrophilic properties. This evidence included testimony that all the hydrophilic excipients in Watson's granules will readily interact with water, testing showing the absorption of water in less than a second, and "contact angle" data determinative of hydrophilicity. (*See* Appx1155 at 17–Appx1156 at 19; Appx1336 at 19–Appx1337 at 9; Appx1193 at 20–Appx1194 at 2; Appx1217 at 1–6; Appx1387 at 3–11; Appx2362; Appx1226 at 21–Appx1227 at 16; Appx1228 at 8–23; Appx1230 at 2–21.)

The district court also found magnesium stearate to be the "main component" of the volume of the granules because it "exhibits the required lipophilic characteristics." (Appx27–28.) The district court adopted Shire's position that the "main component" should not be viewed quantitatively or structurally. (*Id.*) It also accepted Shire's argument that very low concentrations of magnesium stearate should be considered the main component because it is "potent." (Appx28.)

*Second*, on the "outer hydrophilic matrix," the district court relied on the known properties of SSG and images of Watson's ANDA product in aqueous media from Shire's Dr. Steven Little to find that the extragranular volume is hydrophilic. (Appx29–30.) The district court did not specifically address in this discussion the magnesium stearate present in the "outer hydrophilic" matrix volume, and whether it would continue to exhibit its lipophilic characteristics. Nonetheless, the district court concluded that the "extragranular volume exhibits hydrophilic characteristics and does not exhibit lipophilic characteristics." (Appx30.)

*Third*, the district court determined that the volumes of the granules and the extragranular space are spatially and compositionally separate under its constructions, relying primarily on the testimony of Shire's experts and the findings from the 2013 trial. (Appx19–24.) The district court pointed to its

previous finding "that Watson's ANDA product contains two volumes: (1) granules, and (2) the space outside of the granules (the 'extragranular space')," to support its finding that the two matrices are spatially separate. (Appx20.) It also cited new evidence from Dr. Yang as interpreted by Shire's Dr. Patrick Sinko. (Appx21.)

The district court concluded that the two matrix volumes are compositionally separate too because the granules "exhibit lipophilic characteristics" and the extragranular spaces "exhibit hydrophilic characteristics." (Appx22.) The district court also relied on its previous findings regarding the functions of magnesium stearate and SSG within and outside the granules—that "the magnesium stearate would impact release in the granules, but not in the extragranular space," and that, "while the [SSG] outside of the granules would affect release of mesalamine, the [SSG] within the granules would not affect the release." (Appx22 (citing Appx2168 n.25).)

*Fourth*, the district court addressed Watson's argument that "claim 1 excludes excipients from the inner volume of the granule (or, lipophilic matrix) that are not listed in the *Markush* group in claim 1(a), and that claim 1 similarly excludes excipients from the outer volume (or, hydrophilic matrix) that are not listed in the *Markush* group in claim 1(b)." (Appx31.) While the district court acknowledged "the presence of non-claim 1(a) excipients in the granule, and non-

claim 1(b) excipient in the extragranular space," it disagreed that this fact rendered Watson's ANDA product non-infringing. (Appx31–33.) In doing so, the district court committed legal error by turning a "consisting of" limitation into a "comprising" limitation.

On the "consisting of" *Markush* group limitation for the "inner lipophilic matrix," despite finding that 1) "magnesium stearate could not exceed a theoretical maximum of 5%" of the matrix, and 2) the remaining 95-plus percent of "excipients in the volume of the granule were hydrophilic substances"—the district court determined there to be no violation. (Appx32.) It said that "[t]he other hydrophilic excipients—including the sodium starch glycolate—are unrelated to the function of the inner lipophilic matrix." (*Id.*) The district court based this conclusion on Shire's expert testimony "that the hydrophilic compounds in the granules do not affect the overall lipophilic character of that volume—they do not have an effect on the release of mesalamine from the granule." (*Id.*)[6]

[6] The district court also noted in its *Markush* group discussion the "optionally other excipients" element recited in claim 1(c). Despite the fact that "[n]either of the Parties has briefed or argued about how I should construe claim 1(c)," the district court stated without further explanation that this language "tends to support that other excipients within the inner volume and outer volume, which are unrelated to the function of those volumes as inner lipophilic and outer hydrophilic matrices, would be permitted." (Appx32 n.15.) Again, the district court erroneously used the 1(c) language to turn limitations 1(a) and 1(b) into "comprising" limitations.

Similarly, on the *Markush* group limitation for the "outer hydrophilic matrix," the district court agreed that "[m]agnesium stearate, an excipient not within the claim 1(b) *Markush* group, is present within the extragranular space," but found no violation. (Appx33.) The district court's basis for this conclusion was that this magnesium stearate "is overwhelmed by the hydrophilic properties of the [SSG]," and it "does not affect the hydrophilic characteristic of the extragranular space and, thus, is unrelated to the hydrophilic matrix." (*Id.*)

## SUMMARY OF THE ARGUMENT

Judgment should be reversed without remand because the district court refused to apply this Court's construction of a separate "inner lipophilic matrix" and "outer hydrophilic matrix." Under this Court's construction, the undisputed evidence at trial demonstrates that Watson's ANDA product does not meet the "inner lipophilic matrix" limitation of all the asserted claims. Nor does Watson's ANDA product meet the separate "outer hydrophilic matrix" limitation, when construed in accordance with this Court's previous opinion.

The district court deviated in at least three ways from this Court's constructions. *First*, although it recited this Court's requirement that the "lipophilic matrix" itself "cannot have hydrophilic properties," the district court then defied this Court's, the parties', and Shire's own expert's definition of "hydrophilic properties" to find its way to infringement. Specifically, the district

court re-defined "hydrophilic properties" to mean "swelling." It then concluded that the alleged matrix comprised of more than 95% admitted hydrophilic materials was nevertheless a "lipophilic matrix" because it did not swell. Shire's own expert admitted, however, that the alleged matrix exhibited hydrophilic properties, under the ordinary definition of "hydrophilic properties" adopted and agreed by the parties.

*Second*, the district court disregarded this Court's instruction that a matrix is lipophilic if its "main component" is lipophilic. In light of the undisputed evidence that more than 95% of the alleged matrix was comprised of admittedly hydrophilic excipients, the district Court re-defined "main component" to be the component "responsible for the lipophilic . . . behavior." (Appx28.) As applied, the district court's definition is satisfied by any single lipophilic excipient present in the alleged matrix in any amount from 0.0000001% to 100%. In this way, the district court worked its way back to a construction satisfied by the presence of "at least one lipophilic excipient"—that is, the very same construction this Court rejected last time.

*Third*, the district court violated this Court's instruction that the mutually exclusive *Markush* groups of lipophilic and hydrophilic excipients reinforce the compositional separateness of the "lipophilic matrix" from the "hydrophilic matrix." The district court ignored the undisputed evidence of composition—

namely, that the alleged "lipophilic matrix" and "hydrophilic matrix" both contained a mixture of the same lipophilic and hydrophilic excipients in non-trace amounts. Further, as this Court previously explained, the inventors themselves distinguished their invention from a dosage form containing a mixture of lipophilic and hydrophilic excipients throughout. The district court compounded its error by relying on function over composition, citing water drop absorption testing that Shire's own expert conceded was insufficient to establish that any region of Watson's ANDA product was lipophilic.

In addition to the district court's attempts to work around this Court's claim constructions, judgment also should be reversed because the district court legally erred in applying the "consisting of" *Markush* group limitations. Here too, the district court in effect refused to relinquish the "at least one lipophilic excipient" approach that this Court rejected. It did so by simply declaring an exception to the law of "consisting of" for the hydrophilic excipients that made up more than 95% of the alleged lipophilic matrix. But that new exception defies this Court's prior opinion and binding precedent on "consisting of" transitional phrases. The district court further erred in justifying this unprecedented exception to a compositional and structural claim limitation by reference to alleged functional differences.

The judgment should be reversed on multiple grounds in view of the undisputed facts.

## ARGUMENT

### A. Standard of Review

This Court reviews factual findings for clear error and legal conclusions de novo. *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1359 (Fed. Cir. 2007). A finding is clearly erroneous when "the reviewing court on the entire evidence is left with the definite and firm conviction that a mistake has been committed." *United States v. U.S. Gypsum Co.*, 333 U.S. 364, 395 (1948). Underlying claim construction issues are reviewed *de novo* when—as is the case here—the district court did not hear any expert testimony or make other factual findings of extrinsic evidence in construing the patent claims. *Teva Pharm. USA, Inc. v. Sandoz, Inc.*, 135 S. Ct. 831, 841 (2015); *Shire Dev. LLC v. Watson Pharm., Inc.*, 787 F.3d 1359, 1361 (Fed. Cir. 2015). (Appx11–17.)

### B. The District Court Erred Again in Construing "Inner Lipophilic Matrix" and "Outer Hydrophilic Matrix."

The district court's claim constructions on remand failed to follow this Court's instructions. The district court's constructions are thus erroneous, again, and should be reversed, again. But this time there is nothing left for the district court to decide. Applying the claim constructions of this Court to the established and undisputed facts about Watson's ANDA product—including the excipient volume in the granules (the alleged "inner lipophilic matrix") and in the

extragranular space (the alleged "outer hydrophilic matrix")—now necessitates a judgment of non-infringement by this Court.

### 1. The District Court's Claim Construction Violated This Court's Instructions on What It Means to be a "Lipophilic Matrix" That Is Separate from the "Hydrophilic Matrix."

This Court made clear exactly what it meant when it said that the "lipophilic matrix" itself must be lipophilic and separate from the "hydrophilic matrix." It meant that the lipophilic matrix itself "cannot have hydrophilic properties," as a matrix consisting of one lipophilic ingredient and several hydrophilic ingredients would. *Shire*, 787 F.3d at 1367. It also meant that the "main component" of the matrix structure is lipophilic. *Id.* at 1365–66. And it meant that the "lipophilic matrix" does not merely refer to a spatially separate volume as the "hydrophilic matrix" having the same hydrophilic and lipophilic components throughout. *Id.* at 1367. The district court did not heed these instructions. Instead, it applied constructions that are practically the same as the ones this Court already reversed.

The district court first erred when it accepted Shire's invitation to rewrite this Court's decision that "the 'lipophilic' matrix cannot have hydrophilic properties," to mean essentially that the "lipophilic matrix can exhibit hydrophilic properties, just not swelling." (Appx14; Appx26.) The result of the district court's re-construction is that a "lipophilic" matrix can be any matrix that has a lipophilic excipient and numerous hydrophilic excipients, so long as the hydrophilic

excipients do not cause swelling—even though they do readily dissolve, absorb water, and/or exhibit any other hydrophilic properties.

This re-construction is contrary to what this Court actually wrote. This Court's prohibition against hydrophilic properties was unequivocal:

> Thus, the matrix that is deemed the "lipophilic" matrix cannot have hydrophilic properties. But, a matrix comprised of only one lipophilic substance and several hydrophilic substances—and thus capable of exhibiting hydrophilic properties—would meet the district court's construction of "lipophilic matrix." Such a result contradicts the customary and ordinary meaning of "lipophilic" and "hydrophilic."

*Shire*, 787 F.3d at 1367. Nor did this Court limit hydrophilic properties to swelling when it explicitly recognized that "a hydrophilic substance has an affinity for water," which includes the property that "a hydrophilic substance readily dissolves in water." *Shire*, 787 F.3d at 1362 n.1. Thus, the district court's narrowing of "hydrophilic properties" to swelling—and the resultant broadening of what it means to be a "lipophilic" matrix—was in error.

In addition to flouting this Court's controlling definition of "hydrophilic, the district court's re-construction is contradicted by every other articulation of "hydrophilic" properties in this case, by the facts, and even by Shire's own expert. The parties stipulated long ago that "hydrophilic" means "having an affinity to water." (Appx2156.) This stipulated meaning—clearly not limited to swelling—

has never changed. (Appx13.) Even Shire's own expert Dr. Patrick Sinko plainly testified at trial that "hydrophilic" properties are not limited to swelling:

> Q. The function of those three excipients, povidone, copovidone and microcrystalline cellulose, have been known throughout this litigation to be referred to as hydrophilic, yes?
> A. They have an affinity for water, but they don't necessarily swell.
> Q. Okay. Something does not need to swell in order to be hydrophilic, correct?
> A. That's correct.

(Appx1335 at 18–Appx1336 at 1.)

The first and only suggestion that the prohibited "hydrophilic" properties of the "lipophilic matrix" are limited to swelling appeared in Shire's post-trial briefing. Shire theorized: "Therefore, the Federal Circuit's statement that the inner lipophilic matrix 'cannot have hydrophilic properties' at most means that it cannot exhibit the characteristics described in the patent as 'hydrophilic' (*i.e.*, swelling)." (Appx2477.) But as described above and summarized in the table below, Shire's re-definition of "hydrophilic" as "swelling" has no basis in the record.

| Source | Definition of "Hydrophilic" Not Limited to Swelling |
|---|---|
| This Court's June 3, 2015 Decision | "Generally, a lipophilic substance has an affinity for lipids and a hydrophilic substance has an affinity for water. Thus, a lipophilic substance resists dissolving in water, but a hydrophilic substance readily dissolves in water. *See* '720 Patent col. 1 ll. 17-26, 32-36."<br>*Shire*, 787 F.3d at 1362 n.1. |
| The Parties' Construction | "Having an affinity to water"<br>(Appx2156; Appx13.) |
| Shire's Dr. Sinko | Testified that hydrophilic excipients "have an affinity for water, but they don't necessarily swell," and that "[s]omething does not need to swell in order to be hydrophilic."<br>(Appx1335 at 18–Appx1336 at 1.) |

The district court pointed to two excerpts in the patent specification about the use of "hydrophilic matrices" to support its re-construction. (Appx14.) Yet neither of these excerpts, nor any other descriptions in the patent, even suggests that "lipophilic" can encompass all "hydrophilic properties" other than swelling. (*See* Appx37 at 1:21–26, 2:61.) Rather, the cited excerpts describe the known use of hydrophilic matrices to form a "hydrated" or "high viscosity swollen layer." (*Id.*) These disclosures have nothing to do with the required lipophilicity, and thus lack of hydrophilicity, of the "lipophilic matrix."

The district court erred a second time when, recognizing this Court's explanation that the "main component of the matrix" structure is lipophilic in a

"lipophilic matrix," the district court accepted Shire's invitation to re-define the "main component" of a structure to mean the component "responsible for the lipophilic or hydrophilic behavior." (Appx27–28.) This circular construction means that if a structure is designated a "lipophilic matrix," and has just one lipophilic component (which by definition resists water), that structure's "main component" is necessarily its lipophilic one. The parallel "main component" definition for the "hydrophilic matrix" is equally illogical. Thus, in application, the district court's re-definition of "main component" renders its new construction of "lipophilic matrix" to require no more than the old construction, which this Court reversed—namely, only the presence of "at least one lipophilic excipient." *See Shire*, 787 F.3d at 1365, 1368.

A brief illustration demonstrates the absurd consequences of Shire's interpretation of "main component" adopted by the district court. Consider two hypothetical excipient structures—one consisting of 100% hydrophilic excipient X, and the other consisting of 99.9% hydrophilic excipient X and 0.1% lipophilic excipient Y. The 99.9% hydrophilic structure may absorb water relatively more slowly than the 100% hydrophilic structure, because the lipophilic excipient poses a resistance to water in the 0.1% where it exists. Under the district court's rule, the 99.9% hydrophilic composition could be deemed a "lipophilic matrix," and its

"main component" would necessarily be its 0.1% lipophilic component Y. But of course, the "main component" of both structures is hydrophilic excipient X.

The district court could not cite any part of the '720 patent or its prosecution history to support its definition of "main component." (*See* Appx27–28.) Just before its "main component" discussion, however, the district court suggested that a lipophilic matrix having less than 5% lipophilic substances is consistent with the '720 patent because example five "discloses granules containing only 2.4% lipophilic substances by weight." (Appx27 (citing Appx39 at 5:30–45.) This is mistaken. The lipophilic substances in that example comprise 2.4% by weight of the granules *including the 1200 mg mesalamine drug*, but make up 100% of the *excipients* in the granule (*i.e.*, the lipophilic matrix). (Appx39 at 5:30–45.) Indeed, the lipophilic matrices in *all* of the patent examples are made with 100% lipophilic excipients. (Appx38 at 4:9–Appx39 at 5:45.) Neither the patent nor this Court's opinion define "main component" as anything other than its ordinary sense of physical structure or composition. Accordingly, the district court's erroneous "main component" definition is a second independent basis for reversal.

The district court's third claim construction error came when it interpreted this Court's "separateness" requirement to permit infringement by two designated volumes of a tablet that absorb water at different rates, no matter their compositional commonality. While the district court appeared to recognize that

"separate" includes spatial *and* compositional components, its interpretation of the latter was overly broad. (Appx13–14.) The district court's construction interpreted the compositional component to require only "different distributions of excipients that result in separate characteristics." (Appx21.) Thus, the district court's construction looked only to whether two volumes absorbed water at a different undefined rate, and not whether the two volumes shared hydrophilic and lipophilic excipients. This improper interpretation of "separate" also warrants reversal.

According to this Court's mandate, the separateness requirement here involves "mutually exclusive spatial characteristics—one inner, one outer—and mutually exclusive compositional characteristics—one hydrophilic, one lipophilic." *Shire*, 787 F.3d at 1366. The compositional requirement means that the matrices do not share the same lipophilic matrix-forming and hydrophilic matrix-forming ingredients:

> Accordingly, the correct construction requires that the inner volume contain certain substances from the group described for the inner lipophilic matrix (which are all lipophilic substances), and that the outer volume *separately contained* substances from the group described for the outer hydrophilic matrix (which are all hydrophilic).

*Shire*, 787 F.3d at 1367 (emphasis added). To be sure, this Court recognized the possibility of a narrow exception "when there is a trace of hydrophilic molecules in

the inner volume because of a mixing step inherent in the manufacturing process, for example." *Id.* at 1368. But the district court twisted this potential narrow exception beyond recognition.

The district court's construction does not require any inquiry into whether the two volumes *separately* contain their respective matrix-forming substances, per this Court's opinion. Instead, it allows the claims to encompass two spatially separate volumes that have varying concentrations of the *same* lipophilic and hydrophilic excipients, such that each volume will absorb water differently. This construction could even capture two non-identical volumes of the "single mixed matrix with both hydrophilic and lipophilic components" that this Court previously excluded from a correct claim construction. *See Shire*, 787 F.3d at 1367. That is because the district court's approach focuses not on composition, but on the purported relative effects of the excipients in each matrix—*e.g.*, whether the *other* excipients overwhelm magnesium stearate or SSG, respectively. (Appx22; Appx33.) But the district court's reliance on function for the *compositional* claim limitations here is legal error. *See Toro Co. v. White Consol. Indus., Inc.*, 266 F.3d 1367, 1371 (Fed. Cir. 2001) ("An invention claimed in purely structural terms generally resists functional limitation.").

In reality, Shire's "modified" claim constructions adopted by the district court are substantively the same as the ones this Court has already rejected.

Stripping away most of this Court's requirements, these constructions permit a "lipophilic matrix" to be any matrix that exhibits *any* relative resistance to water by virtue of the behavior of the presence of just one lipophilic excipient. Once again, infringement comes down to the mere presence of a single lipophilic excipient. Indeed, the modified constructions still provide for "[a] matrix including at least one lipophilic excipient." (Appx17.) This is precisely the approach that this Court found improper before, and compels reversal again.

### 2. The Correct Constructions from This Court Compel a Finding of Non-Infringement in View of the Undisputed Facts.

This Court should not only reverse on claim construction and remand again, risking a third mistaken finding of infringement. A judgment of non-infringement should be entered as a matter of law. "When we determine on appeal, as a matter of law, that a trial judge has misinterpreted a patent claim, we independently construe the claim to determine its correct meaning, and then determine if the facts presented at trial can support the appealed judgment. If not, we reverse the judgment below without remand for a second trial on the correct law." *Exxon Chem. Patents, Inc. v. Lubrizol Corp.*, 64 F.3d 1553, 1560 (Fed. Cir. 1995). *See also CVI/Beta Ventures, Inc. v. Tura LP*, 112 F.3d 1146, 1161 (Fed. Cir. 1997) (finding that "under the correct claim construction, [the accused infringer was] entitled to a judgment of noninfringement as a matter of law").

Here the proper claim constructions of this Court, in view of the established and undisputed facts, reasonably can only result in non-infringement. Only Shire's literal infringement claims remain.[7] "Literal infringement requires that every limitation in [the asserted] claims be found in the accused product." *Exxon Chem. Patents, Inc.*, 64 F.3d at 1559. Watson's ANDA product plainly does not include a separate "inner lipophilic matrix" and "outer hydrophilic matrix."

As described above, the alleged "lipophilic matrix" undisputedly consists of 40 mg hydrophilic MCC, 48 mg hydrophilic povidone, 42 mg hydrophilic copovidone, some unquantified (but less than 7 mg) amount of lipophilic magnesium stearate, and some unquantified (but less than 34 mg) amount of hydrophilic SSG. (Appx20; Appx2160–62; Appx2209; Appx32.) The purely theoretical maximum concentration of lipophilic magnesium stearate, without factoring SSG into the equation, is 5% by weight of the excipient volume in the granules. (Appx32.) It is therefore established that over 95% by weight of the alleged "inner lipophilic matrix" is made of the four other substances, which are all hydrophilic. (*Id.*) The extragranular volume deemed the "outer hydrophilic matrix" consists of 4 mg colloidal silicon dioxide, some unquantified (but less than

[7] The district court's opinion explains that "Shire orally waived its doctrine of equivalents argument the morning of the 2016 Bench Trial." (Appx10 n.6.)

7 mg) amount of lipophilic magnesium stearate, and some unquantified (but less than 34 mg) amount of hydrophilic SSG. (Appx2162; Appx2209; Appx2341–46.)

The district court's "inner lipophilic matrix" and "outer hydrophilic matrix" violate three requirements of this Court's proper construction, each fatal to infringement. *First*, the accused "lipophilic matrix" structure is not itself lipophilic because it has hydrophilic properties due to its overwhelming majority of hydrophilic excipients. *Second*, the main component of this composition is clearly not lipophilic. *Third*, the two matrices are not compositionally separate because the respective lipophilic and hydrophilic matrix-forming excipients (magnesium stearate and SSG) are mixed throughout the entire tablet.

The excipient volume of the granules plainly has hydrophilic properties according to this Court's opinion. This Court explained that "a matrix comprised of only one lipophilic substance and several hydrophilic substances—and thus capable of exhibiting hydrophilic properties," cannot be the "lipophilic matrix." *Shire*, 787 F.3d at 1365. That is because such a matrix would surely have hydrophilic properties. *Id.*

Here, the hydrophilic excipients in the accused matrix outnumber the lipophilic excipient four to one, and constitute over 95% by weight of the matrix. Shire's experts agreed that povidone, copovidone, and MCC are hydrophilic. (Appx1155 at 17–Appx1156 at 19; Appx1336 at 19–Appx1337 at 9; Appx1458 at

17–Appx1460 at 13.) They also agreed that these three substances do not somehow cease to have hydrophilic properties in Watson's granules. (*Id.*) And of course SSG—the excipient that Shire claims to form a hydrophilic matrix—has hydrophilic properties wherever it appears, including within the granules. (*See* Appx1372 at 14–23.) Thus, *four* hydrophilic excipients capable of exhibiting hydrophilic properties make up over 95% of what the district court held to be the "lipophilic matrix."

As confirmation of these hydrophilic properties of the alleged "lipophilic matrix," Shire's Dr. Yang's conducted water drop testing on cross-sections of Watson's tablet and acknowledged that *all* the tested granules and spaces between the granules showed an affinity for water. (Appx1193 at 20–Appx1194 at 2; Appx1217 at 1–6.) Indeed, Dr. Sinko admitted that all of these volumes absorbed Dr. Yang's water droplets in *less than a second*. (Appx1387 at 3–11.) Even Dr. Yang testified that a longer water penetration time for one material compared to another does ***not*** tell you that the first material is lipophilic. (Appx1218 at 2–12; Appx1232 at 8–17.)

Dr. Yang also recorded and produced for this litigation the "contact angles" of water on Watson's granules which averaged just 28.8 degrees. (Appx2362; Appx1226 at 21–Appx1227 at 16.) Notably, in his published literature on "contact angles" outside of this litigation, Dr. Yang unequivocally wrote that "[w]hen a

material has a contact angle with water less than 90 degrees, that material is hydrophilic or water loving." (Appx1228 at 8–23; Appx1230 at 2–21.) Neither Dr. Yang's 28.8-degree calculated average nor any of his individually recorded contact angles here came remotely close to 90 degrees. (Appx2362; Appx1231 at 17–21.)

In view of the undisputed facts, no one could plausibly say that the 95-plus percent hydrophilic composition alleged to be the "inner lipophilic matrix" in Watson's ANDA product is free from hydrophilic properties. That is why Shire urged a re-definition contrary to the controlling ordinary meaning, such that the district court could ignore the evidence of hydrophilicity here. It is only by accepting Shire's invitation to commit the same legal error it did last time and adopt Shire's "new" constructions, which are effectively the same as those rejected by this Court, that the district court could possibly ignore this undisputed and case-dispositive evidence.

Non-infringement based on the proper application of this Court's "main component" instruction is just as palpable. It belies logic that a component making up less than 5% of a structure or composition is its "main component." This is especially true here where magnesium stearate exists in the granules only because it incidentally penetrates their pores during tableting. (Appx2166–67.) Unlike hydrophilic povidone, copovidone, and MCC, magnesium stearate is not added

during the granulation process. (Appx2160–62; Appx2209; Appx2287–88.) It is also not confined to the granules, but instead is evenly distributed throughout Watson's tablet. (Appx2166; Appx2341–46; Appx1345 at 19–Appx1346 at 6; Appx1435 at 10–14.) And while Shire's experts insisted that magnesium stearate is "potent," none of them could cite a single reference or instance in which anyone in the field has claimed that an excipient making up less than 5% constitutes the "main component" of any structure.

Finally, Watson's ANDA product does not include the claimed compositionally separate "inner lipophilic" and "outer hydrophilic" matrices because the supposed lipophilic and hydrophilic matrix-forming ingredients (magnesium stearate and SSG) are distributed throughout the tablet volume. The district court found the volume of Watson's granules to be the alleged "lipophilic matrix," based on the presence of magnesium stearate in the granules; and the extragranular volume to be a separate "hydrophilic matrix," based on the presence of SSG there**.** (Appx24–26; Appx29–30.) But it is well-established—by Shire's own testing—that both magnesium stearate and SSG are distributed *throughout* the Watson tablet, including the granules and the extragranular space. (Appx2166; Appx2173; Appx2341–46; Appx1346 at 19–Appx1347 at 6.)

No one claims this to be the close call suggested by this Court where the magnesium stearate is present only in "trace amounts" in the extragranular space,

or the SSG is present only in "trace amounts" in the granules. *See Shire*, 787 F.3d at 1368. These two ingredients at issue co-exist throughout both matrix structures. (Appx2166; Appx2173; Appx2341–46; Appx1346 at 19–Appx1347 at 6.) Thus, the two matrices are not compositionally separate, and therefore do not infringe, because they do not "separately contain" their respective matrix-forming excipients.[8]

The correct application of this Court's claim constructions to the undisputed facts is dispositive of non-infringement here for the reasons set forth above. What is more, however, is that on remand Watson offered authoritative pharmaceutical literature confirming that non-infringement under this Court's constructions is consistent with how not only the patent, but also pharmaceutical scientists in the field—including Shire's own experts—describe lipophilic and hydrophilic matrices. For example, Dr. Sinko's own textbook described and depicted the known use of a lipophilic matrix as the drug being distributed "throughout a continuous phase composed of . . . lipid." (Appx1373 at 24–Appx1378 at 5;

[8] To the extent the district court's constructions truly requires compositional separateness, and not just any two volumes having non-identical compositions, the district court still committed legal error because it failed to follow its own constructions. *Ferring B.V. v. Watson Labs., Inc. – Florida*, 764 F.3d 1401, 1411 (Fed. Cir. 2014). Thus, whether because of its erroneous claim construction or infringement finding, the district court's "compositionally separate" determination should be reversed.

Appx1478 at 5–22.) This structure is something entirely different from those in Watson's conventional wet granulation tablet.

The district court dismissed the real-world depictions of lipophilic and hydrophilic matrices as Watson offering "an entirely new construction of 'inner lipophilic matrix' and 'outer hydrophilic matrix.'" (Appx16.) But this was not the case.

To be clear, Watson's claim construction arguments on remand urged only that the district court adopt the ordinary and customary meanings set forth in this Court's opinion. (Appx2434–38.) Those constructions appropriately represented the disputed claim terms' "plain and ordinary meanings to one of skill in the art when read in the context of the specification and prosecution history." *Hill-Rom Servs., Inc. v. Stryker Corp.*, 755 F.3d 1367, 1371 (Fed. Cir. 2014); *Phillips v. AWH Corp.*, 415 F.3d 1303, 1312–13 (Fed. Cir. 2005). They also nullify the district court's infringement determination.

### C. The District Court's Determinations That the Matrix Structures Satisfy the Respective "Consisting of" *Markush* Group Limitations Should Be Reversed.

As a result of the erroneous claim constructions, in particular the continued inclusion of the "at least one lipophilic [or hydrophilic] excipient" language, the district court found that the compositions of the alleged "inner lipophilic matrix" and "outer hydrophilic matrix" further satisfy these terms' *Markush* groups

limitations. (*See* Appx31–33.) This determination not only defies this Court's guidance on remand, it also contradicts this Court's long-standing jurisprudence on "consisting of" transitional phrases. It is therefore clearly erroneous. *See Ferring B.V. v. Watson Labs., Inc. – Florida*, 764 F.3d 1401, 1411 (Fed. Cir. 2014) (finding reversible error because the infringement finding below "was not in accordance with law").

A proper infringement analysis on the *Markush* group limitations could reasonably only lead to non-infringement. The asserted claims require that each matrix "consists of" only the specified hydrophilic or lipophilic substances in its respective *Markush* group. (Appx39 at 6:10–25.) This Court's mandate explicitly recognized and provided guidance on these *Markush* group limitations. *Shire*, 787 F.3d at 1367. And the controlling precedent is clear—the use of "consisting of" precludes any elements outside of those listed, unless the additional elements are merely impurities or are wholly unrelated. *Conoco, Inc. v. Energy & Envtl. Int'l, L.C.*, 460 F.3d 1349, 1360 (Fed. Cir. 2006); *Norian Corp. v. Stryker Corp.*, 363 F.3d 1321, 1331–32 (Fed. Cir. 2004).

Here, significant amounts of substances outside the listed *Markush* group are present in the alleged matrices—for example, the hydrophilic excipients making up *over 95%* of the alleged "lipophilic matrix." (Appx32; Appx1341 at 1–24; Appx2209; Appx1335 at 1–5.) No one claims these substances to be impurities.

Nor can these chemical substances, particularly in such high concentrations, be dismissed under the narrow "unrelated" exception. The district court's contrary finding would upend decades of fundamental "consisting of" patent law and should be reversed.

### 1. The Legal Scope of the "Consisting of" *Markush* Group Limitations Described in this Court's 2015 Opinion.

This Court's June 3, 2015 opinion explicitly recognized that "[t]he compositions of the inner volume and outer volume, *i.e.*, inner matrix and outer matrix, respectively, are further limited by the *Markush* groups." *Shire*, 787 F.3d at 1367. Specifically, claim 1 of the '720 patent requires an "inner lipophilic matrix ***consisting of substances selected from the group consisting of*** unsaturated and/or hydrogenated fatty acid, salts, esters or amides thereof, fatty acid mono-, di- or triglycerids, waxes, ceramides, and cholesterol derivatives . . . ." (Appx39 at 6:10–17 (emphasis added).) It further requires an "outer hydrophilic matrix" that "***consists of compounds selected from the group consisting of*** polymers or copolymers of acrylic or methacrylic acid, alkylvinyl polymers, hydroxyalkyl celluloses, carboxyalkyl celluloses, polysaccharides, dextrins, pectins, starches and derivatives, alginic acid, and natural or synthetic gums . . . ." (Appx39 at 6:18–25.) This Court confirmed that the substances enumerated in the "lipophilic matrix" *Markush* group are all lipophilic, and that those for the "hydrophilic matrix" are all hydrophilic. *Shire*, 787 F.3d at 1367. No one disputes this.

It is well-established that the transitional phrase "consisting of" excludes elements, steps, or ingredients not specified in the claim. *AFG Indus., Inc. v. Cardinal IG Co., Inc.*, 239 F.3d 1239, 1245 (Fed. Cir. 2001); *Vehicular Techs. Corp. v. Titan Wheel Int'l, Inc.*, 212 F.3d 1377, 1382–83 (Fed. Cir. 2000). When the phrase "consisting of" introduces a clause of the claim, it limits the element set forth in that clause. *Mannesmann Demag Corp. v. Engineered Metal Prods. Co., Inc.*, 793 F.2d 1279, 1282 (Fed. Cir. 1986). Such exclusion is not absolute, however, as "consisting of" does not exclude ordinarily associated impurities. *Conoco, Inc. v. Energy & Envtl. Int'l, L.C.*, 460 F.3d 1349, 1360 (Fed. Cir. 2006). Nor does "consisting of" exclude additional components or steps that are "unrelated" to the claim or claim limitation. *Norian Corp. v. Stryker Corp.*, 363 F.3d 1321, 1331–32 (Fed. Cir. 2004).

The "unrelated" exception to the exclusionary effect of "consisting of" was articulated in *Norian*, 363 F.3d at 1331–32. In *Norian*, this Court held that the presence of a spatula was "irrelevant" to a kit "consisting of" bone repair chemicals and, accordingly, was not excluded from the scope of the claims. *See id.* The Court in *Norian* reasoned that infringement cannot be "avoided by the presence of a spatula, for the spatula has no interaction with the chemicals, and is irrelevant to the invention." *See id.* at 1332.

*Norian*, however, also recognized that *no other chemical* could be included in the "consisting of" chemical composition as claimed. *Norian*, 363 F.3d at 1331 ("The invention is a kit containing specified chemicals, and the claims are explicitly limited in that no other chemical can be included in the composition."); *id.* at 1332 ("the term 'consisting of' permits no other chemicals in the kit"). This understanding is rooted in long-standing patent law. *See In re Gray*, 53 F.2d 520, 521 (C.C.P.A. 1931) (ruling that a composition "consisting of silver and . . . indium" was limited to "an alloy of silver and indium without other elements"). This Court more recently confirmed the narrow scope of the "unrelated" exception in *Digene Corp. v. Third Wave Technologies, Inc.*, 323 F. App'x 902, 909 (Fed. Cir. 2009). In *Digene*, the Court held that the addition of *any* DNA, outside the DNA specified in the "consists of" group at issue, warranted a finding of non-infringement. *Id.* Notably, this Court has never suggested that any function of additional unlisted chemicals could render such additions "unrelated" to a closed "consisting of" group of chemicals.

The district court appeared to incorporate this narrow "unrelated" legal exception into its construction of the *Markush* groups transitional phrases for the "inner lipophilic matrix" and "outer hydrophilic." (Appx2195.) It construed "selected from the group consisted of" to mean "an exclusionary term specifying that an element contains only what is expressly set forth in a recited list, but does

not exclude substances unrelated to, or outside of the context of said element." (*Id.*) Yet in its infringement determinations here, the district court improperly stretched the narrow exception to swallow the "consisting of" rule, and turn the phrases into "comprising" phrases. This error is yet another casualty of the district court's decision to double-down on its rejected "at least one lipophilic [or hydrophilic] excipient" approach on remand.

### 2. The District Court Legally Erred in Finding the "Consisting of" *Markush* Group Limitation of Lipophilic Excipients to Permit No Fewer Than Four Hydrophilic Excipients Making Up More Than 95% of the Alleged "Lipophilic Matrix."

Despite this Court's long-standing "consisting of" precedent, the district court held that the inclusion of *four* non-compliant hydrophilic excipients in the "lipophilic matrix" still did not warrant a finding of non-infringement. (Appx31–33.) This finding is clearly erroneous, as a matter of law.

It is undisputed that the hydrophilic povidone, copovidone, and MCC comprising at least 95% of the district court's "inner lipophilic matrix" are *not within this term's Markush group.* (Appx1155 at 13–Appx1156 at 7; Appx1334 at 23–Appx1335 at 5; Appx1457 at 1–Appx1459 at 5.) In addition to these three excipients, some amount of hydrophilic SSG—also outside the exclusionary *Markush* group—is present in the alleged "lipophilic matrix." (Appx1346 at 19–Appx1347 at 2.) Indeed, the district court even acknowledged that these "[o]ther excipients, not within the claim 1(a) *Markush* group are present within the inner

volume" (*i.e.*, the "inner lipophilic matrix"). (Appx33.) It nevertheless refused to find that these non-claim 1(a) excipients result in non-infringement.

At the outset, the district court disagreed that under this Court's opinion there can be no infringement "when the volume of the inner lipophilic matrix contains one lipophilic substance and several hydrophilic substances." (Appx31.) The district court appeared to suggest that this Court's prior reversal and remand somehow re-defined "consisting of," against this Court's long-standing precedent, to allow significant amounts of "non-claim 1(a) excipients in the granule" and "non-claim 1(b) excipients in the extragranular space." (*See id.*) In other words, that this Court implicitly blessed the district court's "at least one lipophilic excipient" approach, even as to the *Markush* groups. (*See id.*; Appx1817 at 14–Appx1820 at 6.) This suggestion again defies the controlling mandate here. *See Laitram Corp. v. NEC Corp.*, 115 F.3d 947, 951 (Fed. Cir. 1997) ("[T]he district court's actions on remand should not be inconsistent with either the letter or the spirit of the mandate.").

In the first appeal, this Court reversed and remanded for the district court to determine, according to this Court's instructions, whether Watson's ANDA product includes the claimed matrices consistent with their respective *Markush* groups. *Shire*, 787 F.3d at 1368. This Court also provided explicit guidance on a possible exception to non-infringement that comports with the controlling law of

"consisting of"—where there are "trace of hydrophilic molecules in the inner volume because of the mixing step inherent in the manufacturing process, for example." *Id.* *Nothing* in this Court's prior opinion indicates, either explicitly or implicitly, that non-trace amounts of hydrophilic excipients are acceptable as "unrelated" in the "inner lipophilic matrix."

Moreover, the undisputed facts here should have mooted any question about this Court's "trace amounts" exception on which the district court relied. No one claims that these four hydrophilic excipients are present in only trace amounts. Nor are these hydrophilic excipients present in the district court's "lipophilic matrix" because of a mixing step inherent to manufacturing. Rather, the hydrophilic excipients outside the "consisting of" group here are at least 95% of the inner matrix. (Appx32; Appx1334 at 12–Appx1337 at 3, 1341 at 1–24.) Indeed, the povidone and copovidone were included as binders, and the MCC as a filler, for the very purpose of making the granules. (Appx2160–62; Appx2209; Appx2287–89; Appx1367 at 18–Appx1368 at 1.) Thus, the district's court's reliance on the potential non-infringement exception expressed by this Court was clearly mistaken. (*See* Appx31.)

**a) The District Court Erred as a Matter of Law in Finding That the Hydrophilic Excipients Making Up the Overwhelming Majority of the Matrix Structure Are "Unrelated."**

The district court ultimately concluded that the "other hydrophilic excipients—including the [SSG]—are unrelated to the function of the inner lipophilic matrix." (Appx32.) That conclusion was on its face legally erroneous. It also perpetuates the same mistaken "at least one lipophilic excipient" approach that this Court reversed in the prior appeal.

Here, as in *Norian*, the exclusionary "consisting of" group of chemical substances for the "lipophilic matrix" means that "no other chemical can be included" (putting aside impurities). *Norian*, 363 F.3d at 1331. The patentees chose to define their invention by explicitly excluding any non-trace hydrophilic chemical substances within the "lipophilic matrix." (Appx39 at 6:10–17.) The hydrophilic substances in the purported "inner lipophilic matrix" in Watson's ANDA are in violation of this prohibition. The clear result is non-infringement.

Neither this Court's 2004 *Norian* decision nor its progeny permit additional chemicals outside a compositional "consisting of" group to be ignored as "unrelated." In fact, this Court's subsequent 2005 decision in *Norian* confirmed this understanding. *Norian Corp. v. Stryker Corp.*, 432 F.3d 1356 (Fed. Cir. 2005). There the claim limitation at issue recited "a solution consisting of water and a sodium phosphate." *Id.* at 1358. This Court found that the "consisting of" phrase

there precluded even the addition of a second type of sodium phosphate, and affirmed summary judgment of non-infringement on that basis. *Id.* at 1362–63. This Court did *not* see it fit to consider whether the additional chemical could be deemed "unrelated" by virtue of whether it affected the general characteristics or function of the solution. *Id.* The same approach is appropriate for the "consisting of" chemical restrictions in this case. The hydrophilic excipients here are akin to the necessarily-related additional sodium phosphate in the 2005 *Norian* decision, not the unrelated spatula in the 2004 *Norian* decision.[9]

Even more striking here, however, the non-compliant *hydrophilic* substances in the inner matrix are the *antithesis* of the *lipophilic* substances to which the claimed matrix is restricted. Such hydrophilic substances are thus far more than merely "related." Indeed, SSG is the very excipient found to drive the opposing "outer hydrophilic matrix" in Watson's ANDA product. (Appx29–30.) Accordingly, no reasonable fact finder could conclude that hydrophilic SSG, povidone, copovidone, and MCC—making up over 95% by weight of the district court's lipophilic matrix—have "no interaction with" or "are irrelevant to" the lipophilic matrix. *See Norian*, 363 F.3d at 1331–32.

[9] The non-compliant hydrophilic substances here are also like the additional DNA in *Digene* leading to non-infringement—such additional DNA could not be deemed "unrelated" to the "consisting of" limitation based on whether and how it affected the overall function or properties. *Digene*, 323 F. App'x at 909.

The district court's infringement analysis essentially treated the "consisting of" phrase—well-understood and construed to signal exclusion—as an open "comprising" term. The phrase "comprising" is "inclusive or open-ended and does not exclude additional, unrecited elements or method steps." *CIAS, Inc. v. Alliance Gaming Corp.*, 504 F.3d 1356, 1360 (Fed. Cir. 2007). By finding that over 95% of the chemicals in the alleged lipophilic matrix could be ignored, the district court transformed the "unrelated" exception into free license to include additional elements, as if the "lipophilic matrix" merely "comprised" of certain lipophilic substances. As explained above, that is not the controlling law of the "consisting of" phrase applicable here.

Not to belabor the point, but the district court's erroneous claim construction and subsequently flawed infringement analysis would not have been appropriate even for a "consisting *essentially* of" limitation, which "represents a middle ground between the open-ended term 'comprising' and the closed-ended phrase 'consisting of." *AK Steel Corp. v. Sollac and Ugine*, 344 F.3d 1234, 1239 (Fed. Cir. 2003). "Consisting essentially of" is a phrase that "has long been understood to permit inclusion of components not listed in the claim, provided that they do not 'materially affect the basic and novel properties of the invention.'" *Id.* Here the district court's findings about relative lipophilicity and effects on mesalamine release could not legally transform the composition of 95% *hydrophilic* substances

even to one "consisting *essentially* of" certain *lipophilic* substances. Such findings certainly cannot upend the obvious non-infringement of the more restrictive "consisting of" limitations at issue here.

In summary, the district court's disregard of the four hydrophilic substances within the "inner lipophilic matrix" as "unrelated" was legally erroneous, as it directly conflicts with this Court's precedent regarding the closed effect of "consisting of" transitional phrases. Although the district court's exclusionary construction appeared to recognize this effect, the district court's analysis did not follow its own claim construction. That too was reversible error. *See Ferring B.V.*, 764 F.3d at 1411.

**b) The District Court Erroneously Based Its "Unrelated" Conclusion on the Function of Each Excipient in the Structure of the Purported "Inner Lipophilic Matrix."**

Even if an "unrelated" exception was legally appropriate here under this Court's precedent, the district court's focus on the hydrophilic excipients' relation to function, over composition or structure, was improper. The district found the four hydrophilic substances to be "unrelated" because they "do not have an effect on the release of mesalamine from the granule" and "do not affect the lipophilic characteristics of the inner volume," unlike the lipophilic magnesium stearate in the granules. (Appx32–34.) In other words, the district court concluded that "the other excipients, besides magnesium stearate, in the granules are *functionally*

unrelated to the lipophilic matrix." (Appx26 n.12 (emphasis added).) The district court could make no findings that the four hydrophilic excipients are "unrelated" to the *structure or composition* of the "inner lipophilic matrix." The district court's purely functional basis for its "unrelated" determination was legal error.

The claimed "inner lipophilic matrix" is purely structural or compositional, formed only of certain specified chemicals. (Appx39 at 6:7–42.) It is not defined in the claims by its function, and therefore should not be interpreted as having functional requirements. *See Schwing GmbH v. Putzmeister Aktiengesellschaft*, 305 F.3d 1318, 1324 (Fed. Cir. 2002) ("Where a claim uses clear structural language, it is generally improper to interpret it as having functional requirements."); *Toro Co*, 266 F.3d at 1371. Thus, the district court legally erred in finding that because the hydrophilic excipients did not function within the "inner lipophilic matrix" to affect the release rate of mesalamine, they must be "unrelated." (*See* Appx32–34; Appx26 n.12.) These findings as to function or effect are irrelevant to the closed compositional and structural claim limitations. *See Cross Med. Prods., Inc. v. Medtronic Sofamor Danek, Inc.*, 424 F.3d 1293, 1319 (Fed. Cir. 2005) ("[W]e agree with Cross Medical that the function served by the crown member is irrelevant to finding that this structural limitation is met.").

In the proper structural and compositional context, the four hydrophilic excipients cannot credibly be considered "unrelated." They are over 95% of the

matrix composition. Three of them—povidone, copovidone, and MCC—are added during granulation for the very purpose of *creating the structure* deemed the "inner lipophilic matrix." (Appx2160–62; Appx2209; Appx2287–89; Appx1367 at 18–23.) In fact, Shire's Dr. Sinko testified at trial that the hydrophilic povidone and copovidone are the very substances that "help the granules stick together." (Appx1367 at 18–23.) Moreover, notwithstanding the district court's arbitrary distinctions of the *function* of SSG within and outside the granules, as a chemical matter, there is no difference between any of this SSG. (*See* Appx32 n.14; Appx1372 at 19–23.)

The district court's functional analysis resembles what might have been relevant to the doctrine of equivalents, but certainly not the *literal* infringement inquiry here. Under the doctrine of equivalents, of course, if a limitation is not literally satisfied, the patentee may present evidence that the accused element performs substantially the same function, in substantially the same way, to achieve substantially the same result. *Ring & Pinion Serv., Inc. v. ARB Corp. Ltd.*, 743 F.3d 831, 835 (Fed. Cir. 2014). But as the district court found, Shire waived its doctrine of equivalents assertions prior to the start of trial. (Appx10 n.6.) Thus, the *only* question now is whether the accused "lipophilic matrix" composition is limited to the claimed "consisting of" substances. The answer is clearly no.

Accordingly, the alleged "inner lipophilic matrix" of excipients in Watson's granules is not a "lipophilic matrix consisting of substances selected from the group consisting of" the lipophilic substances recited in the *Markush* group of subsection (a) of claim 1. The district court's conclusion otherwise requires reversal in favor of non-infringement.

### 3. The District Court Legally Erred in Finding That the Inclusion of Magnesium Stearate in the "Outer Hydrophilic Matrix" Was Not Dispositive of Non-Infringement.

The district court's erroneous construction of the "outer hydrophilic matrix," especially its continued "at least one hydrophilic excipient" approach, likewise led it to conclude that the presence of magnesium stearate in the extragranular volume (*i.e.*, the district court's "outer hydrophilic matrix") does not violate the *Markush* group limitation of claim 1(b). (Appx33.) The district court found that "the magnesium stearate in the extragranular space is overwhelmed by the hydrophilic properties of the [SSG]," rendering it legally "unrelated to the hydrophilic matrix." (*Id.*)

This "unrelated" infringement finding is also clearly erroneous, for the same reasons as the lipophilic matrix limitation. It is undisputed that magnesium stearate is not one of the hydrophilic substances listed in the *Markush* group for the "outer hydrophilic matrix." No one claims magnesium stearate to be present in the outer matrix in "trace amounts" or as an impurity. Nor could they, as Watson

added the magnesium stearate extragranularly after the granules were formed. (Appx2160–62; Appx2209; Appx2287–88.) And given the chemical "consisting of" limitation at issue here, the addition of this non-compliant substance cannot be "unrelated" as a matter of law. *Norian*, 363 F.3d at 1331–32; *Digene*, 323 F. App'x at 909; *Gray*, 53 F.2d at 521. Even if it could, the district court's sole reliance on the *function* of magnesium stearate in the extragranular space rather than its relation to composition or structure was also legal error, given that Shire waived its doctrine of equivalents arguments before trial. *See Southwall Techs., Inc. v. Cardinal IG Co.*, 54 F.3d 1570, 1575, 1579 (Fed. Cir. 1995) (Unlike the doctrine of equivalents, which permits infringement by showing substantially the same function, way, and, result, "[t]o establish literal infringement, every limitation set forth in a claim must be found in an accused product, exactly.") The district court's contradictions of fundamental patent law cannot stand.

Finally, the district court improperly tried to bolster its incorrect "unrelated" conclusions by referencing in a footnote the "optionally other excipients" language in claim 1(c). (Appx32 n.15.) Neither party had presented evidence at trial or argument in post-trial briefing as to this other claim element. The district court permitted only Shire to address it in the extraordinary "rebuttal" closing argument that the district court gave Shire. (Appx1843; Appx1850 at 2–Appx1852 at 5.) Even then, Shire did not rely on this language for its position. (*Id.*)

In any event, the claim 1(c) language provides no help to the district court's errors here. The district court defined the "inner lipophilic matrix" in Watson's ANDA product as the entire excipient composition in the granules, and the "outer hydrophilic matrix" as the excipient composition in the extragranular volume. (Appx21; Appx24; Appx29–31; Appx33.) The excipients in those volumes are therefore, by the district court's own terms, not something "other" than those in the claimed matrices.

Under the proper "consisting of" analysis, the inclusion of the lipophilic magnesium stearate in the alleged "outer hydrophilic matrix" also results in non-infringement. Magnesium stearate is not only outside the "hydrophilic matrix" *Markush* group, it belongs to the opposite and "mutually exclusive" *Markush* group for the "lipophilic matrix." (Appx39 at 6:10–17; Appx2166 n.19; Appx2162 n.9.) *Shire*, 787 F.3d at 1366–67. And Shire's experts agree that there is no chemical difference between the supposed lipophilic matrix-forming magnesium stearate inside the granules, and the magnesium stearate in the extragranular space. (Appx1157 at 1–16.) Thus, magnesium stearate is a substance in direct conflict with, and certainly not "unrelated" to, the claimed "outer hydrophilic matrix." Because both claim limitations at issue recite closed "consisting of" restrictions, rather than a more permissive transitional phrase, Watson's ANDA product cannot reasonably be found to infringe.

## CONCLUSION

This Court should reverse the district court's claim construction of "inner lipophilic matrix" and "outer hydrophilic matrix" and hold that under the proper constructions, according to this Court's June 3, 2015 opinion in the prior appeal, Watson's ANDA product does not infringe because it does not include the claimed "inner lipophilic matrix" and/or "outer hydrophilic matrix."

Alternatively, and independently, this Court should reverse the district court's judgment of infringement based on the district court's legally erroneous determinations that the alleged "inner lipophilic matrix" and "outer hydrophilic matrix" in Watson's ANDA product do not violate the respective *Markush* groups further limiting the chemical compositions of the matrix structures.

Respectfully submitted,

**MADDOX EDWARDS, PLLC**

Dated: May 4, 2016

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# ADDENDUM

# ADDENDUM

**Page No.**

**UNITED STATES DISTRICT COURT**
**SOUTHERN DISTRICT OF FLORIDA**

**CASE NO. 12-60862-CIV-MIDDLEBROOKS/BRANNON**

SHIRE DEVELOPMENT LLC,
SHIRE PHARMACEUTICAL
DEVELOPMENT INC.,
COSMO TECHNOLOGIES LIMITED and
GIULIANI INTERNATIONAL LIMITED,

Plaintiffs,

v.

WATSON PHARMACEUTICALS, INC.,
WATSON LABORATORIES, INC. –
FLORIDA, WATSON PHARMA, INC., and
WATSON LABORATORIES, INC.,

Defendants.
_____/

**FINAL JUDGMENT**

In accordance with this Court's March 25, 2016 Opinion and Order, and the undisturbed findings of the Court's 2013 Order (DE 246), it is hereby

**ORDERED AND ADJUDGED** that Final Judgment is **ENTERED** in favor of Plaintiffs[1] and against Defendants[2] as follows:

1. U.S. Patent No. 6,773,720 (the "'720 Patent") is not invalid under 35 U.S.C. § 112 for lack of written description and/or enablement.
2. The filing of Abbreviated New Drug Application ("ANDA") No. 203817 was an act of infringement of the '720 Patent by Defendants.

[1] "Plaintiffs" refers to: Shire Development LLC; Shire Pharmaceutical Development, Inc.; Cosmo Technologies Limited; and Nogra Pharma Limited (f/k/a Giuliani International Limited).
[2] Defendants" refers to: Actavis, Inc. (formerly Watson Pharmaceuticals, Inc.); Watson Laboratories, Inc. – Florida; Watson Pharma, Inc.; and Watson Laboratories, Inc.

3. Any commercial manufacture, use, sale, offer for sale, and/or importation in the United States of the products that are the subject of ANDA No. 203817 by Defendants prior to the expiration of the '720 Patent will constitute an act of infringement of the '720 Patent.
4. The effective date of any approval of the product that is the subject of ANDA No. 203817 shall be no earlier than the date on which the '720 Patent expires.
5. Defendants are preliminarily and permanently enjoined from engaging in the commercial manufacture, use, sale, offer for sale, and/or importation in the United States of the products that are the subject of ANDA No. 203817 prior to the expiration of the '720 Patent.
6. Watson Pharmaceuticals, Inc. has, is, and will induce and/or contribute to Watson Laboratories, Inc.—Florida's, Watson Pharma, Inc.'s, and Watson Laboratories, Inc.'s infringement of the '720 patent.
7. The commercial manufacture, use, sale, offer for sale and/or importation into the United States of any products that are the subject of ANDA No. 203817 would induce and/or contribute to third-party infringement of the '720 patent.

**DONE AND ORDERED** in Chambers at West Palm Beach, Florida, this 25 day of March, 2016.

DONALD M. MIDDLEBROOKS
UNITED STATES DISTRICT JUDGE

Copies to: Counsel of Record

**UNITED STATES DISTRICT COURT**
**SOUTHERN DISTRICT OF FLORIDA**

**CASE NO. 12-60862-CIV-MIDDLEBROOKS/BRANNON**

SHIRE DEVELOPMENT LLC,
SHIRE PHARMACEUTICAL
DEVELOPMENT INC.,
COSMO TECHNOLOGIES LIMITED and
GIULIANI INTERNATIONAL LIMITED,

Plaintiffs,

v.

WATSON PHARMACEUTICALS, INC.,
WATSON LABORATORIES, INC. –
FLORIDA, WATSON PHARMA, INC., and
WATSON LABORATORIES, INC.,

Defendants.
_____/

**OPINION AND ORDER**

THIS CAUSE comes before the Court upon the Federal Circuit's Mandate issued September 1, 2015, which remanded this case for further proceedings in accordance with the Federal Circuit Opinion. (DE 305). Plaintiffs[1] (collectively, "Plaintiffs" or "Shire") assert that Defendants[2] (collectively, "Defendants" or "Watson") infringe claims 1 and 3 of United States Patent 6,773,720 (the "'720 Patent"). I held a bench trial on the remaining issues for disposition

[1] Shire Development LLC, Shire Pharmaceutical Development Inc., Cosmo Technologies Limited, and Nogra Pharma Limited (f/k/a Giuliani International Limited).
[2] Watson Pharmaceuticals, Inc. (n/k/a Actavis, Inc.) ("Watson Pharmaceuticals"), Watson Laboratories, Inc. – FL (n/k/a Actavis Laboratories FL, Inc.) ("Watson Florida"), Watson Pharma, Inc. (n/k/a Actavis Pharma, Inc.) ("Watson Pharma"), and Watson Laboratories, Inc. ("Watson Laboratories") (collectively, "Watson").

from January 25 through January 27, 2016, with closing arguments held on March 23, 2016. Based on the evidence presented, I make the following finds of fact and conclusions of law.[3]

## I. Procedural Background

**'720 Patent.** The '720 Patent is listed in the FDA's publication titled "Approved Drug Products with Therapeutic Equivalence Evaluations" (commonly known as the "Orange Book") as covering Lialda®. Shire Development is the owner of New Drug Application ("NDA") No. 22000, and is FDA-approved for the manufacture and sale of mesalamine delayed-release tablets containing 1.2 g mesalamine, which are commercialized under the tradename Lialda®. Lialda® is indicated for the induction of remission in adults with active, mild-to-moderate ulcerative colitis and for the maintenance of remission of ulcerative colitis.

**Complaint.** On May 8, 2012, Plaintiffs filed this action for infringement of the '720 Patent against Defendants under the Hatch-Waxman Act (the "Hatch-Waxman Act" or the "Act"), 35 U.S.C. § 271.

The Hatch-Waxman Act permits a generic drug manufacturer to obtain approval to market a generic version of a previously approved pharmaceutical product without conducting expensive and time-consuming tests to establish the safety and effectiveness of that product. In place of these safety and efficacy tests, the generic manufacturer must submit an Abbreviated New Drug Application ("ANDA") to the Federal Drug Administration ("FDA") and demonstrate that its product is bioequivalent to the branded product. 21 U.S.C. § 355(j)(2)(A)(iv). The Hatch-Waxman Act requires that an ANDA applicant submit a "Paragraph IV" certification in its ANDA, certifying that the product it seeks FDA approval to market will not infringe any valid

[3] To the extent that any findings of fact constitute conclusions of law, they are hereby adopted as such; to the extent that any conclusions of law constitute findings of fact, they are also so adopted.

U.S. patent. *Id.* § 355(j)(2)(A)(vii)(IV). The Act also requires that an ANDA applicant submit a detailed notice to the patent owner, known as a "Paragraph IV notice," explaining the factual and legal basis for the opinion that the patent is invalid or that the generic product will not infringe the patent. *Id.* § 355(j)(2)(B); *see also* 21 C.F.R. § 314.95(c)(6). The patent owner may file a suit for patent infringement within forty-five days of receipt of a Paragraph IV notice. If the owner files suit, then the FDA may not approve the ANDA for thirty months or until a United States court finds for the defendant based on non-infringement, patent invalidity, or patent unenforceability. *Id.* § 355(j)(5)(B)(iii).

Defendant Watson Florida submitted Watson's ANDA number 203817 ("ANDA Product") to the FDA seeking approval to engage in the commercial manufacture, use, sale, offer for sale, and/or importation of Watson's ANDA Product. Watson's ANDA Product is a generic mesalamine delayed-release tablet and contains 1.2 g mesalamine as the active ingredient.

Watson's ANDA included a "Paragraph IV" certification seeking FDA approval before the expiration of the '720 Patent. On March 26, 2012, pursuant to 21 U.S.C. § 355(j)(2)(B)(iv), Watson sent the Paragraph IV certification to Cosmo Technologies Limited, Young & Thompson, Shire US Inc., and "Shire." Watson's notice indicates that Watson Florida seeks FDA approval to market Watson's ANDA Product before the '720 Patent expires.

Plaintiffs filed their Complaint against Defendants on May 8, 2012, within forty-five days of receipt of the Paragraph IV notice letters, and filed an Amended Complaint (DE 43) on August 3, 2012. Plaintiffs allege infringement of one or more claims of the '720 Patent against all Defendants (Count I), and induced and/or contributory infringement of the '720 Patent by Watson Pharmaceuticals (now Actavis) (Count II). With regard to Count II, Plaintiffs allege that Watson Pharmaceuticals knowingly induced Watson Pharma, Watson Laboratories, and/or

Watson Florida to infringe and/or contributed to Watson Pharma's, Watson Laboratories', and/or Watson Florida's infringement of the '720 Patent. They also allege that Watson Pharmaceuticals actively induced, encouraged, aided, or abetted Watson Pharma's, Watson Laboratories', and/or Watson Florida's preparation, submission, and filing of Watson's ANDA with a Paragraph IV certification to the '720 Patent. Plaintiffs assert that these acts constitute infringement under 35 U.S.C. § 271.

On August 23, 2012, Defendants filed their Answer. (DE 52). Within the Answer, Watson Florida asserts two counterclaims for declaratory relief: (1) a declaration that their ANDA Product would not infringe any claim of the '720 Patent, (*see* DE 52 at 15-16); and (2) a declaration that the '720 Patent and its claims are invalid under 35 U.S.C. § 112, for lack of written description and lack of enablement, to the extent the claims are alleged to cover any products set forth in the Watson ANDA. (*See* DE 52 at 16-17).

**Claims at Issue.** Plaintiffs are asserting infringement of only claims 1 and 3 of the '720 Patent. Claim 1 is the '720 Patent's only independent claim, and provides:

> 1. Controlled-release oral pharmaceutical compositions containing as an active ingredient 5-amino-salicylic acid, comprising:
>
> a) an inner lipophilic matrix consisting of substances selected from the group consisting of unsaturated and/or hydrogenated fatty acid, salts, esters or amides thereof, fatty acid mono-, di- or triglycerids, waxes, ceramides, and cholesterol derivatives with melting points below 90° C., and wherein the active ingredient is dispersed both in said the lipophilic matrix and in the hydrophilic matrix;
>
> b) an outer hydrophilic matrix wherein the lipophilic matrix is dispersed, and said outer hydrophilic matrix consists of compounds selected from the group consisting of polymers or copolymers of acrylic or methacrylic acid, alkylvinyl polymers, hydroxyalkyl celluloses, carboxyalkyl celluloses, polysaccharides, dextrins, pectins, starches and derivatives,

> alginic acid, and natural or synthetic gums;
>
> c) optionally other excipients;
>
> wherein the active ingredient is present in an amount of 80 to 95% by weight of the total composition, and wherein the active ingredient is dispersed both in the lipophilic matrix and in the hydrophilic matrix.

'720 Patent at col.6 11.7-30.

Claim 3, which is dependent on claim 1, recites: "Compositions as claimed in claim 1, in the form of tablets, capsules, mintablets." (*Id.*).[4]

**2013 Markman Hearing and Trial.** At the request of the Parties, and following claim construction briefing and a *Markman* hearing on December 20, 2012, I issued an Order dated January 16, 2013 (DE 147), construing certain disputed claims of the '720 Patent.

I held a non-jury trial from April 8 through April 12, 2013, with closing arguments conducted on April 26, 2013 ("2013 Trial"). Following the 2013 Trial, I entered an Opinion and Order (DE 246, "2013 Order"), finding that Watson's ANDA Product infringed claims 1 and 3 of the '720 Patent. Specifically, I found that Watson's ANDA Product met the limitations of the claims that were at issue. I further found that the claims were not invalid under 35 U.S.C. § 112 for lack of a written description or enablement. I held that Shire was entitled to injunctive relief.

**Federal Circuit Appeal.** Following the 2013 Order, Watson appealed to the United States Federal Circuit. On appeal, Watson challenged the 2013 constructions of the claim terms "inner lipophilic matrix" and "outer hydrophilic matrix," and, thus, my subsequent infringement finding. Watson did not otherwise challenge the 2013 claim construction Order or appeal any of the other factual findings supporting the infringement determination in the 2013 Order.

[4] Because claim 3 is dependent on claim 1, it necessarily contains all of the limitations of claim 1. Thus, Watson's ANDA Product can only infringe claim 3 if it infringes claim 1. Said differently, if Watson's ANDA Product does not infringe claim 1, it cannot infringe claim 3.

On March 28, 2014, the Federal Circuit issued an opinion, affirming my construction of the term "matrix," but reversing my construction of "inner lipophilic matrix" and "outer hydrophilic matrix." *Shire Dev. LLP v. Watson Pharms. Inc.*, 746 F.3d 1326 (Fed. Cir. 2014) [hereinafter *Watson I*].

Shire appealed the Federal Circuit's Order in *Watson I* to the U.S. Supreme Court, arguing that the Federal Circuit did not give proper deference to my factual findings underlying claim construction. Petition for a Writ of Certiorari, *Shire Dev., LLC, v. Watson Pharms., Inc.*, 135 S. Ct. 1174 (2015) (No. 14-206). The Supreme Court granted Shire's petition for certiorari, vacated *Watson I*, and remanded for proceedings consistent with *Teva Pharmaceuticals USA, Inc. v. Sandoz, Inc.*, 135 S. Ct. 831 (2015). *Shire Dev., LLC v. Watson Pharms., Inc.*, 135 S. Ct. 1174 (2015).

The parties engaged in supplemental briefing on remand to the Federal Circuit, and the Federal Circuit re-issued its opinion on June 3, 2015. *Shire Dev., LLC v. Watson Pharms., Inc.*, 787 F.3d 1359 (Fed. Cir. 2015) [hereinafter *Watson II*]. In *Watson II*, the Federal Circuit held *Watson I* did not implicate factual findings to which it owed deference under *Teva*. The Federal Circuit then reaffirmed its reversal of my construction of "inner lipophilic matrix" and "outer hydrophilic matrix," as well as the reversal of the associated infringement finding.

**2016 Trial.** I held a bench trial on January 25 through January 27, 2016, to adjudicate the remaining issue—whether the accused Watson tablet[5] infringes the claimed "inner lipophilic matrix" and "outer hydrophilic matrix" limitations of the asserted claims, when those terms are construed in accordance with the Federal Circuit's Mandate.

[5] The formulation for which Watson currently seeks FDA approval remains the same as the formulation from the 2013 Trial. *See* 2016 Trial Tr. Day 1 at 200:20-24, Sinko Direct.

## II. Law of Infringement

Pursuant to 35 U.S.C. § 271(e)(2), it is an act of infringement

> to submit [an ANDA] for a drug claimed in a patent or the use of which is claimed in a patent . . . if the purpose of such submission is to obtain approval under such Act to engage in the commercial manufacture, use, or sale of a drug . . . claimed in a patent . . . before the expiration of such patent.

*Id.* Within the Hatch-Waxman context, the act of infringement that gives rise to a case or controversy has been noted as "artificial," as the specific infringing composition has not yet been made, used, or sold. *Glaxo, Inc. v. Novopharm, Ltd.*, 110 F.3d 1562, 1569 (Fed. Cir. 1997) (citing *Eli Lilly & Co. v. Medtronic, Inc.*, 496 U.S. 661, 675, 677 (1990)). In these cases, "[t]he relevant inquiry is whether the patentee has proven by a preponderance of the evidence that the alleged infringer will likely market an infringing product." *Id.* at 1570. That said, "[w]hat is likely to be sold, or, preferably, what will be sold, will ultimately determine whether infringement exists." *Id.*

"Whoever actively induces infringement of a patent shall be liable as an infringer." 35 U.S.C. § 271(b). Additionally, 35 U.S.C. § 271(c) provides for contributory infringement:

> Whoever offers to sell or sells within the United States or imports into the United States a component of a patented machine, manufacture, combination or composition . . . constituting a material part of the invention, knowing the same to be especially made or especially adapted for use in an infringement of such patent, and not a staple article or commodity of commerce suitable for substantial noninfringing use, shall be liable as a contributory infringer.

*Id.* at § 271(c).

Patent infringement is a question of fact, and a patent is infringed if a single claim is infringed. *Cephalon, Inc. v. Watson Pharms., Inc.*, 707 F.3d 1330, 1340, (Fed. Cir. 2013); *Intervet Am., Inc. v. Kee-Vet Labs., Inc.*, 887 F.2d 1050, 1055 (Fed. Cir. 1989). It is well established that the infringement analysis involves two steps. "First, the court determines the

scope and meaning of the patent claims asserted . . . and then the properly construed claims are compared to the allegedly infringing device." *Cybor Corp. v. FAS Techs., Inc.*, 138 F.2d 1448, 1454 (Fed. Cir. 1998). "To prevail, the plaintiff must establish by a preponderance of the evidence that the accused device infringes one or more claims of the patent either literally or under the doctrine of equivalents."[6] *Bayer AG v. Elan Pharm. Research Corp.*, 212 F.3d 1241, 1247 (Fed. Cir. 2000) (citing *Insituform Techs., Inc. v. Car Contracting, Inc.*, 161 F.3d 668, 692 (Fed. Cir. 1998)).

**Literal Infringement.** "To prove literal infringement, a plaintiff must show that the accused device contains each and every limitation of the asserted claims." *Presidio Components, Inc. v. Am. Technical Ceramics Corp.*, 702 F.3d 1351, 1358 (Fed. Cir. 2012) (citing *Uniloc USA, Inc. v. Microsoft Corp.*, 632 F.3d 1292, 1301 (Fed. Cir. 2011)). This may be done with direct or circumstantial evidence, and a patentee need not present direct evidence of infringement. *O2 Micro Int'l Ltd. v. Beyond Innovation Tech. Co., Ltd.*, 449 F. App'x 923, 928 (Fed. Cir. 2011) (citing *Lucent Techs., Inc. v. Gateway, Inc.*, 580 F.3d 1301, 1318 (Fed. Cir. 2009); *Symantec Corp. v. Computer Assocs. Int'l, Inc.*, 522 F.3d 1279, 1293 (Fed. Cir. 2008)). Further, it is improper to compare the accused product with a preferred embodiment in the examples of the patent, instead of with the claims. *See SRI Int'l v. Matsushita Elec. Corp. of Am.*, 775 F.2d 1107, 1121 (Fed. Cir. 1985) (citations omitted). "If any claim limitation is absent from the accused device, there is no literal infringement as a matter of law." *Id.* (quoting *Bayer AG*, 212 F.3d at 1247).

[6] Shire originally argued that Watson's ANDA Product infringed literally and under the doctrine of equivalents. However, Shire orally waived its doctrine of equivalents argument the morning of the 2016 Bench Trial. Accordingly, I will only consider whether Watson's ANDA product literally infringes the '720 Patent.

## III. Claim Construction in light of the Federal Circuit Mandate

### a. Prior Constructions

Following the *Markman* Hearing, in my January 16, 2013 Order (DE 147), I construed the following terms:[7]

| Claim Term | 2013 Construction |
|---|---|
| "inner lipophilic matrix" | a matrix including at least one lipophilic excipient, where the matrix is located within one or more other substances |
| "outer hydrophilic matrix" | a matrix of at least one hydrophilic excipient, where the matrix is located outside the inner lipophilic matrix |

Applying these constructions, I found that Watson's ANDA Product contained both an inner lipophilic matrix and outer hydrophilic matrix. Defendant Watson appealed my construction of these terms, and the Federal Circuit reversed my constructions. *See Watson II*, 737 F.3d at 1365.

### b. Federal Circuit Mandate

The Federal Circuit upheld my construction of "matrix" as "a macroscopically homogenous structure in all its volume." *Watson II*, 787 F.3d at 1365. With respect to the claim constructions of "inner lipophilic matrix" and "outer hydrophilic matrix," the Parties disagree about what the Federal Circuit held.

For the reasons discussed below, I find that the Federal Circuit held that: (1) each matrix must exhibit "lipophilic" or "hydrophilic" properties, respectively, and (2) the matrices must be "separate" from each other. *Id.* at 1365-68.

[7] I construed additional disputed and agreed upon claim terms in the claim construction Order (DE 147), which were not disturbed on appeal. Accordingly, I incorporate the definition and discussion of those terms by reference. *See* 2013 Order at 5-6.

**c. The Lipophilic Matrix Must Exhibit Lipophilic Characteristics and the Hydrophilic Matrix Must Exhibit Hydrophilic Characteristics**

The Federal Circuit held that the inner matrix must exhibit lipophilic characteristics and the outer matrix must exhibit hydrophilic characteristics. *Watson II*, 787 F.3d at 1365-66 (Section III.A of the opinion). Specifically, the Federal Circuit held that the adjective "lipophilic" means that "the matrix—not just an excipient within the matrix—must exhibit the stipulated-to lipophilic properties." *Id.* The Federal Circuit explained that "the '720 patent teaches that this occurs when 'the main component of the matrix structure' is lipophilic." *Id.* (citing PTX001 at 1:17-18).

For the meaning of "lipophilic characteristics," the Federal Circuit looked to the patent specification. *See Watson II*, 787 F.3d at 1365. Specifically, the Federal Circuit cited to the passage describing lipophilic characteristics as providing "some resistance to the penetration of the solvent due to the poor affinity towards aqueous fluids." *Id.* at 1367 (referring to '720 Patent at col.1 ll. 17-20). The Federal Circuit also observed that the Parties stipulated that "lipophilic" means "poor affinity towards aqueous fluids." *See Watson II*, 787 F.3d at 1365.

The intrinsic record also provides insight into the meaning of "hydrophilic characteristics," even though the Federal Circuit does not provide express guidance as it does for "lipophilic characteristics." For example, the '720 Patent's specification describes "high resistance to the progress of the solvent" caused by the presence of "strongly hydrophilic groups" that "remarkably increases viscosity inside the hydrated layer." ('720 Patent at col.1 ll.22-26). In another passage, the '720 Patent describes hydrophilic characteristics as the formation of "a high viscosity swollen layer." (*Id.* at col.2 ll.60-64). Furthermore, the specification states that the substances that constitute the hydrophilic matrix are known as "hydrogels." (*Id.* at col.3 ll.18-23; *see also id.* at col.3 l.57-col.4 l.5) (describing the dissolution characteristics of the outer

hydrophilic matrix)). Additionally, the Parties have stipulated that "hydrophilic" means "having an affinity to water." (2013 Order at 6).

**d. The Lipophilic and Hydrophilic Matrices Must Be Separate**

The Federal Circuit also held that the inner lipophilic matrix and the outer hydrophilic matrix must be "separate." *Watson II*, 787 F.3d at 1366-68. The Federal Circuit held that "[t]he prosecution history, the structure of the claim itself, the ordinary meaning of the claim terms, including the Markush group limitations, and the patent's description of the invention compel a claim construction which requires that the inner lipophilic matrix is *separate* from the outer hydrophilic matrix." *Id.* at 1366 (emphasis added).

The ordinary meaning of the claim terms provides one basis for the Federal Circuit's holding of separate matrices. *Watson II*, 787 F.3d at 1366-67. For example, the Federal Circuit observed that the individual words "inner" and "outer" define "mutually exclusive spatial characteristics," and the words "lipophilic" and "hydrophilic" define "mutually exclusive compositional characteristics." *Id.* at 1366. Under the Federal Circuit's reasoning, "*one* matrix cannot be both inner and outer in a relation to a second matrix. Nor can *one* matrix be both hydrophilic and lipophilic." *Id.* at 1367 (emphasis added). Consequently, a single structure may not serve as both a lipophilic matrix and a hydrophilic matrix. *See id.* at 1366-67. Thus, the Federal Circuit concluded that the ordinary meaning of the claim terms requires "the inner volume to be separate from the outer volume." *Id.*

The Federal Circuit further concluded that the "lack of overlap" between the two Markush groups[8] in the claim "supports the requirement that the *volumes* be separate." *Watson II*, 787 F.3d at 1367 (emphasis added).

In addition, the Federal Circuit found that the description of the invention in the specification also provides support for its holding that the matrices be separate. *Watson II*, 787 F.3d at 1367. The Federal Circuit explained that the examples in the '720 Patent describe "discrete lipophilic matrix granules" compressed with the hydrophilic matrix. *Id.* Thus, the "discrete" granules are one example of an inner volume that is spatially separate from an outer volume (*i.e.*, the extragranular space). *Id.* at 1367.

The Federal Circuit also explained that the specification describes separate compositional characteristics. *Watson II*, 787 F.3d at 1367. For an illustration of "compositional" lipophilic characteristics, the Federal Circuit cited the specification, which describes "some resistance to the penetration of solvent due to the poor affinity towards aqueous fluids." *Id.* Additionally, as described above, the specification describes compositional hydrophilic characteristics as "remarkably increase[d] viscosity inside the hydrated layer" or "a high viscosity swollen layer."' ('720 Patent at col.1 ll.21-26; *id.* at col.2 l.61). Therefore, the Federal Circuit's statement that the inner lipophilic matrix "cannot have hydrophilic properties" means that it cannot exhibit the characteristics described in the patent as "hydrophilic." *Watson II*, 787 F.3d at 1367.

In addition, the Federal Circuit explained that claim constructions that could encompass a single matrix structure of lipophilic and hydrophilic excipients would be too broad. *Watson II*, 787 F.3d at 1367-68. The Federal Circuit observed that "any arbitrarily selected volume in a

[8] "A Markush group lists specified alternatives in a patent claim, typically in the form: a member selected from the group consisting of A, B, and C." *Watson II*, 787 F.3d at 1363 n.3 (citing *Gillette Co. v. Energizer Holdings, Inc.*, 405 F.3d 1367, 1372 (Fed. Cir. 2005)).

single mixed matrix would satisfy the district court's construction of 'inner lipophilic matrix' because that volume would necessarily contain 'at least one lipophilic excipient' and it would be 'inside' the surrounding volume." *Id.* at 1367. Again, the Federal Circuit reasoned that a *single* structure cannot serve as both a lipophilic matrix and a hydrophilic matrix. *Id.* The Federal Circuit concluded that the claims "require *two* matrices with a defined spatial relationship." *Id.* at 1368 (emphasis added).

**e. Construction of "inner lipophilic matrix" and "outer hydrophilic matrix" on Remand**

Governed by the Federal Circuit's Mandate on remand, I face a limited task. On remand, I must follow the Federal Circuit's Mandate as the law of the case. *Cardiac Pacemakers, Inc. v. St. Jude Med., Inc.*, 576 F.3d 1348, 1356 (Fed. Cir. 2009) ("The mandate rule requires that the district court follow an appellate decree as the law of the case."). Here, the Federal Circuit's Mandate states:

> [W]e reverse the district court's constructions of 'inner lipophilic matrix' and 'outer hydrophilic matrix,' and its subsequent infringement determination, and we remand for proceedings consistent with this opinion.

*Watson II* at 1368. Thus, the "proceedings" described by the Mandate require me to determine whether the Watson product contains an "inner lipophilic matrix" and an "outer hydrophilic matrix," consistent with the Federal Circuit's Opinion.

At the 2016 Trial, Shire argued that the proper construction of "inner lipophilic matrix" and "outer hydrophilic matrix" are apparent from the Federal Circuit's Opinion. Specifically, Shire contends that the Federal Circuit simply imposed two additional requirements on the previous constructions of "inner lipophilic matrix" and "outer hydrophilic matrix": the two

matrices must exhibit their respective lipophilic or hydrophilic characteristics, and the two matrices must be separate. (2016 Trial Tr. Day 1 at 12:7-20, Shire Opening).

In contrast, Watson urges me to adopt an entirely new construction of "inner lipophilic matrix" and "outer hydrophilic matrix." Watson argues that "lipophilic matrix" means a "dispersion of an active ingredient within a continuous phase of water insoluble material which forms a lipophilic structure with an active ingredient packed into the interstices of that structure." (2016 Trial Tr. Day 1 at 51:3-6, Watson Opening). Similarly, Watson argues that "hydrophilic matrix" means a "dispersion of active ingredient and a sufficiently large amount of swelling hydrophilic materials known as hydrogels, which, upon coming into contact with liquid swell to form and maintain a gel layer around the dosage form." (*Id.* at 53:10-14, Watson Opening). Watson contends that these two constructions are consistent with the ordinary and customary meaning of "lipophilic matrix" and "hydrophilic matrix," and that these constructions are consistent with the Federal Circuit's requirements. (*Id.* at 52:3-7, Watson Opening).

I am not convinced by Watson's argument that the newly-proposed constructions should be adopted. For starters, Watson did not argue on appeal that the 2013 constructions were incorrect due to their failure to account for the plain meaning set forth in its new constructions. Additionally, Watson's constructions are different than it proposed to the Federal Circuit on appeal. (Br. of Defs.-Appellants at 35). On appeal, Watson argued that the inner lipophilic matrix should be construed as "a lipophilic matrix that is separate and distinct from, and contained within, an outer hydrophilic matrix." (Br. of Defs.-Appellants at 35). Similarly, Watson argued that the outer hydrophilic matrix should be construed as "a hydrophilic matrix that is separate and distinct from, and external to, an inner lipophilic matrix." (*Id.*).

Notably, Watson's construction of these terms on appeal align—for the most part— with Shire's proposed constructions on remand; namely, that "the respective matrices themselves need to be 'lipophilic' (*i.e.* have a 'poor affinity towards aqueous fluids') or 'hydrophilic,' (*i.e.* have an 'affinity to water')." (*Id.* at 43).

I find that the Federal Circuit's treatment of the proper constructions of these terms forecloses any new constructions. *See Engel Industries, Inc. v. Lockformer Co.*, 166 F.3d 1379 (Fed. Cir. 1999) ("An issue that falls within the scope of the judgment appealed from but is not raised by the appellant in its opening brief is necessarily waived. Unless remanded by this court, all issues within the scope of the appealed judgment are deemed incorporated within the mandate and thus are precluded from further adjudication."). Here, the remand was narrow, and for the purpose of determining whether Watson's ANDA Product meets the Federal Circuit's requirements that: (1) the inner lipophilic matrix must exhibit lipophilic characteristics, (2) the outer hydrophilic matrix must exhibit hydrophilic characteristics, and (3) the matrices must be separate.

Accordingly, "inner lipophilic matrix" and "outer hydrophilic matrix" are construed as follows:

| **Claim Term** | **2016 Construction on Remand** |
|---|---|
| "inner lipophilic matrix" | a matrix including at least one lipophilic excipient, where the matrix exhibits lipophilic characteristics and is located within, and separate from, the outer hydrophilic matrix |
| "outer hydrophilic matrix" | a matrix of at least one hydrophilic excipient, where the matrix exhibits hydrophilic characteristics and is located outside of, and separate from, the inner lipophilic matrix. |

On remand, I must determine whether Watson's product satisfies these additional limitations.

## IV. Infringement Analysis

Having determined the proper construction of "inner lipophilic matrix" and "outer hydrophilic matrix," I must now determine, as a matter of fact, whether Shire has proven that Watson's product has an "inner lipophilic matrix" and "outer hydrophilic matrix" when properly construed.

In determining whether Watson's ANDA Product contains an "inner lipophilic matrix" and "outer hydrophilic matrix," as Shire argues, I must consider whether the ANDA Product has: (1) two separate matrices; (2) an inner lipophilic matrix that exhibits lipophilic characteristics; and (3) an outer hydrophilic matrix that exhibits hydrophilic characteristics.

### a. Undisturbed Findings of Fact

Claim 1 requires a "[c]ontrolled-release oral pharmaceutical composition[] containing as an active ingredient 5-amino-salicylic acid." ('720 Patent at col.6 ll.7-8). Claim 1 also requires active ingredient "in an amount of 80 to 95%." (*Id.* at col.6 ll.27-28). Watson does not dispute that its ANDA Product is a controlled-release oral pharmaceutical composition in the form of a tablet (2013 Order at 13-15), which contains 5-amino-salicylic acid as an active ingredient (*Id.* at 12 n.12), in an amount of 80-95% by weight of the total composition. (DE 325-1, Joint Pretrial Stip., at ¶ 29).

Additionally, I made the following undisturbed findings in my 2013 Order (DE 246) that are relevant to my consideration of whether Watson's ANDA Product contains an "inner lipophilic matrix" and "outer hydrophilic matrix" as those terms are now defined:[9]

1. Magnesium stearate in the granules forms a macroscopically homogeneous structure in all of its volume. (*Id.* at 16).

2. Sodium starch glycolate in the extragranular volume forms a macroscopically homogenous structure in all its volume. (*Id.* at 23).

3. Active ingredient mesalamine is dispersed in both the "inner lipophilic matrix" and "outer hydrophilic matrix" of Watson's ANDA Product. (*Id.* at 24-26).

4. The magnesium stearate located in the granules of the Watson ANDA Product slows the release of mesalamine. (*Id.* at 22).

5. The sodium starch glycolate located in the extragranular space will affect the release of mesalamine. (*Id.* at 18 n.25).

**b. Inner Lipophilic Matrix and Outer Hydrophilic Matrix are Separate**

As discussed above, the Federal Circuit held that the constructions of "inner lipophilic matrix" and "outer hydrophilic matrix" require separate matrices. *Watson II*, 787 F.3d at 1366. The Federal Circuit explained that "the matrices are defined by mutually exclusive spatial characteristics—one inner, and one outer—and mutually exclusive compositional characteristics—one hydrophilic, one lipophilic." *Id.* at 1366. The Federal Circuit described "spatial characteristics" in terms of different volumes. *Id.* at 1367 ("the construction of 'inner lipophilic matrix' requires the inner volume to be separate from the outer volume."); *see also id.* (the Markush group "supports the requirement that the volumes be separate"). The Federal Circuit described "compositional characteristics" in terms of the characteristics of the matrices

[9] Additional relevant findings of fact to the infringement determination were made in the 2013 Order, and remain the law of the case. (2013 Order).

described by the patent. *See also id.* ("[t]he specification explains that a lipophilic matrix 'opposes some resistance to the penetration of the solvent due to the poor affinity towards aqueous fluids'").

For the reasons discussed below, the Watson ANDA Product contains a spatially and compositionally separate inner lipophilic matrix and outer hydrophilic matrix.

**i. Spatially Separate**

I previously found that Watson's ANDA Product contains two volumes: (1) granules, and (2) the space outside of the granules (the "extragranular space"). (2013 Order at 16-17, 18 at n.25, 23). I based this finding on evidence from Dr. Bugay, who conducted Scanning Electron Microscopy ("SEM") and Energy Dispersive X-Radiation ("EDX") analysis on the uncoated, core tablets used in Watson's ANDA Product. (*Id.* at 16; PTX 42, SEM-EDX Images). I also considered Watson's manufacturing process, which results in compressed tablets made up of granular and extragranular regions. (2013 Order at 11-12).

At the 2016 Trial, Dr. Steven Little testified that Dr. Bugay's images depicted inner and outer volumes that were spatially separate: "You can see discrete regions that are granules here that are different than and separate from the extragranular space . . . so they are spatially separate." (2016 Trial Tr. Day 1 at 73:5-9; *see also id.* 72:21-73:9, 83:6-14, Little Direct). Similarly, Dr. Patrick Sinko testified that the images show the granules and extragranular space "are spatially separate, so they are physically separate . . . ." (*Id.* at 230:8-9, Sinko Direct). Additionally, Watson's expert, Dr. Park, acknowledged that Watsons's ANDA Product was divided into granular and extragranular volumes. (2016 Trial Tr. Day 2 at 283:25-239:18, Park Cross).

Additionally, Shire presented evidence from Dr. Yang that further shows Watson's ANDA Product contains two separate volumes. (2016 Trial Tr. Day 1 at 152:7-20). Dr. Yang microtomed[10] a Watson ANDA tablet, and examined the cross-sectioned surface with an optical microscope. Dr. Yang observed two spatially separate structures, which he identified as "Type 1" and "Type 2." "Type 1" structures were generally oval or circular in shape and had a darker coloring. "Type 2" structures were generally between the "Type 1" structures and were irregularly shaped with lighter coloring. (*Id.* at 144:9-15; 147:25-148:21). Dr. Sinko later testified that the "Type 1" and "Type 2" structures were the "granular" and "extra-granular" regions, respectively. *See id.* at 217:10-218:16 ("[Dr. Yang] called them type one and type two . . . I typically refer[] to them [as] granular and extra-granular. But basically, it is the same thing.").

Accordingly, Shire's proposed inner lipophilic and outer hydrophilic matrices are defined by mutually exclusive spatial characteristics, as the volume making up the inner lipophilic matrix—the interior of the granules—is spatially separate from the volume making up the outer hydrophilic matrix—the extragranular space.

**ii. Exhibit Separate Characteristics**

I must next consider whether the spatially separate volumes—the inner granules and the extragranular space—exhibit separate characteristics. Evidence presented at trial shows that the separate inner and outer volumes contain different distributions of excipients that result in separate characteristics. This separate distribution of excipients accounts for the separate characteristics (*i.e.* lipophilic and hydrophilic) exhibited by each of the matrices.

[10] A microtome is an advanced cutting instrument, which Dr. Yang used to obtain a very smooth surface, upon which he conducted a drop penetration test. (2016 Trial Tr. Day 1 at 144:2-8, Yang Direct).

I previously found the hydrophilic sodium starch glycolate exists in clusters or aggregates, indicating higher concentration, in the extragranular spaces of Watson's ANDA tablet, as compared to the granular spaces. (2013 Order at 23). Additionally, based on Dr. Bugay's SEM/EDX images, Dr. Sinko testified that there are no aggregates of sodium starch glycolate inside the granule. (2016 Trial Tr. Day 2 at 75:18-76:1, Sinko Redirect). Dr. Sinko testified that sodium starch glycolate is more "potent than the mag stearate outside" and that "it's separate because it overwhelms the behavior of the mag stearate." (2016 Trial Tr. Day 1 at 224:3-21, Sinko Direct).

As I previously found, the magnesium stearate would impact release in the granules, but not in the extragranular space. (2013 Order at 18 n. 25). Further, I found that, while the sodium starch glycolate outside of the granules would affect release of mesalamine, the sodium starch glycolate within the granules would not affect the release. (*Id.*). This differential in the distribution of excipients results in two separate volumes that exhibit separate characteristics: the granules exhibit lipophilic characteristics whereas the extragranular regions exhibit hydrophilic characteristics. (*Id.* at 72:16-73:24, Little Direct; *id.* at 228:20-230:16, Sinko Direct).

Additionally, Dr. Little testified at the 2016 Trial that he observed two volumes that exhibit two separate characteristics during his dissolution studies of the Watson ANDA Product.[11] First, the outer regions of the Watson ANDA tablet began to swell, erode, and disintegrate. (2016 Trial Tr. Day 1 at 82:20-83:14, Little Direct). As this occurred, intact granules were released. (*Id.*). Dr. Little explained that the swelling, erosion, and disintegrating behavior of the extragranular regions is due to the outer hydrophilic matrix of sodium starch glycolate. (*Id.* at 82:10-15). In contrast, the granules that were released throughout the

[11] I addressed Dr. Little's experimental method in my 2013 Order, and those findings were undisturbed on appeal. (DE 246 at 14-15).

dissolution observation did not swell, but instead persisted in the buffer. Dr. Little explained that the persistence of the granules is due to the magnesium stearate within the inner volume of the granules. (*Id.* at 86:16-87:20). Dr. Little testified that "the two different behaviors that we see are different, they are separate. So you see a hydrophilic behavior, and then what is inside is you see these granules that are exhibiting lipophilic behavior." (*Id.* at 82:20-85:11).

Dr. Yang also presented experimental evidence of two volumes exhibiting compositionally separate matrices. Dr. Yang performed a water penetration test to assess whether the Watson ANDA Product contained separate volumes that exhibit different capacities to resist the penetration of water. (*Id.* at 140:14-141:12, Yang Direct). A drop penetration test is a routine test used to study the interactions between solid and liquid. (*Id.* at 141:6-12, Yang Direct; *see also* 2016 Trial Tr. Day 1 at 218:17-21, Sinko Direct (drop penetration test is a standard characterization tool recognized by pharmaceutical industry)).

As described above, Dr. Yang microtomed a tablet, within which he identified ten "Type 1" and ten "Type 2" locations. (2016 Trial Tr. Day 1 at 147:25-149:19, Yang Direct). Then, Dr. Yang used a microgoniometer to place picoliter-sized drops of distilled water on each type of structure. (*Id.* at 150:11-152:2, 161:6-7). The microgoniometer measured the penetration rate of the drops deposited on the "Type 1" and "Type 2" regions. (*Id.* at 155:10-156:4). On average, the "Type 1" granules exhibited a water penetration rate that was *6.8-times slower* than the "Type 2" extragranular regions. (*Id.* at 152:4-154:15; PTX 512 at 8). Thus, Dr. Yang's experimental data also shows that the "Type 1" and "Type 2" structures exhibit separate compositional characteristics regarding affinity for water.

Accordingly, I find that the inner volume of the granules and the extragranular volume—which make up the volume of Shire's proposed "inner lipophilic matrix" and "outer hydrophilic matrix," respectively—exhibit compositionally separate characteristics.

**c. Inner Lipophilic Matrix Exhibits Lipophilic Characteristics**

I must next determine whether the Watson ANDA Product contains an inner lipophilic matrix that exhibits lipophilic characteristics. As described above, the Federal Circuit explained that the '720 Patent described "lipophilic properties" as "some resistance to the penetration of the solvent due to the poor affinity towards aqueous fluids." ('720 Patent at col.1 ll.17-20; *Watson II*, 787 F.3d at 1365). Additionally, the Parties stipulate to a construction of "lipophilic" that means "having a poor affinity toward aqueous fluids." (2013 Order at 6). The '720 Patent also describes that the inner lipophilic matrix slows the release of mesalamine. ('720 Patent col.4 l.1-5). The inquiry, therefore, is whether the inner volume of the granules—which is the volume that meets the "separate" requirement—exhibits these lipophilic characteristics.

My undisturbed findings of fact support that the distribution of magnesium stearate in the volume of the granules exerts resistance to the penetration of solvent. First, it is undisputed that magnesium stearate is a lipophilic substance. (2013 Order at 12 n.9, 16 n.19). Additionally, I previously found that "magnesium stearate located in the granules will have an effect on the release of mesalamine." (*Id.* at 18 n.25; *see also id.* at 22 n.31). Furthermore, I found that the effect on release by magnesium stearate was linked to its lipophilic characteristics: "[magnesium stearate is] known to perform the function of slowing drug release by virtue of [its] lipophilic nature." (*Id.* at 22). In fact, the only way that magnesium stearate controls release is due to its lipophilic characteristics. (2016 Trial Tr. Day 1 at 215:19-216:5, Sinko Direct).

Furthermore, testimony showed that magnesium stearate may impart lipophilic characteristics to a composition even in low concentrations. Dr. Sinko testified that "very low concentrations [of magnesium stearate] have been known to have significant effects on tablet formulations." (*Id.* at 208:23-209:8). Dr. Sinko discussed scientific literature recognizing that fluid completely failed to penetrate a blend containing 5% magnesium stearate. (*Id.* at 209:12-22, 210:25-211:24). Dr. Sinko also discussed references where a concentration of 0.5% magnesium stearate would have "a pretty significant effect increasing that complete dissolution time by . . . eight, ten, plus fold." (*Id.* at 211:25-213:17). Defendant's expert Dr. Park also acknowledged that "being lipophilic is a reason that magnesium stearate may retard the release . . . ." (2016 Trial Tr. Day 2 at 197:22-25, Park Cross).

Additionally, Dr. Yang's experimental testing confirms that the granules exhibit a poor affinity for aqueous fluids. As described above, Dr. Yang found that the absorption rate of water was 6.8 times slower into the Type 1 structure (the granules) compared to the absorption rate of water into the Type 2 structure (the extragranular region). (2016 Trial Tr. Day 1 at 154:12-15, 155:12-18, 156:17-157:2, Yang Direct; *id.* at 214:8-14, 219:11-17, Sinko Direct).

Although magnesium stearate is present with other excipients inside of the granule—specifically, povidone, copovidone, and microcrystalline cellulose—those other excipients are not responsible for the lipophilic characteristics observed in the granules. During the first trial, Shire presented the testimony of Watson's expert Dr. Leo Trevino, who performed a dissolution test on Watson's milled granules. (2013 Order at 22 n.31; 2013 Trial Tr. Day 3 at 205:20-207:13, Sinko Direct). These granules contained mesalamine and the same excipients (povidone, copovidone, and microcrystalline cellulose) as the granules in the final compressed Watson ANDA Product. However, the granules Dr. Trevino tested lacked magnesium stearate and

sodium starch glycolate. (*Id.* at 10:7-11:3, Trevino Direct; *id.* at 206:6-207:4, Sinko Direct). In the absence of magnesium stearate and sodium starch glycolate, Dr. Trevino's test showed near-immediate release of mesalamine from the milled granules. (*Id.* at 207:5-13, Sinko Direct). Similarly, Dr. Little performed a dissolution experiment with pure mesalamine and observed that the mesalamine dissolved within seconds to minutes. (2016 Trial Tr. Day 1 at 84:18-22, 86:3-15, Little Direct; *see also* 2013 Order at 14-15). Given these results, Drs. Little and Sinko concluded that something in the Watson granules besides the intragranular excipients (povidone, copovidone, and microcrystalline cellulose) was slowing the release of the mesalamine. (2013 Order at 15; 2013 Trial Tr. Day 2 at 39:22-40:2, Little Cross; 2016 Trial Tr. Day 1 at 86:16-87:20, Little Direct; *id.* at 214:15-24, 216:19-217:9, Sinko Direct).[12]

Dr. Little's dissolution experiment—discussed above and in the 2013 Order—also provides evidence that the inner volume of the Watson ANDA Product exhibits resistance to the penetration of solvent. (2013 Order at 14-15; 2016 Trial Tr. Day 1 at 86:12-15, Little Direct). Dr. Little testified that the granules released from the Watson ANDA Product did not swell—thus, they did not exhibit hydrophilic characteristics—as they would if the sodium starch glycolate in the granules had any effect. (*Id.* at 82:23-83:14, 85:8-11, Little Direct; 2013 Order at 15 n.25). Rather, the granules resisted the penetration of the aqueous buffer and persisted for as long as 86 minutes. (2013 Order at at 15; 2016 Trial Tr. Day 1 at 84:13-17, 86:12-15, 87:16-20, Little Direct; *id.* at 214:15-24, 216:17-217:9, Sinko Direct). Based on the high solubility of mesalamine and Dr. Trevino's test showing that the other hydrophilic ingredients had no effect

[12] This evidence also supports that the other excipients, besides magnesium stearate, in the granules are functionally unrelated to the lipophilic matrix. This is discussed in more detail in Section IV. e.

on release, Dr. Little concluded that magnesium stearate is responsible for the granules' resistance to dissolution. (*Id.* at 83:15-19, 86:16-87:20, Little Direct).

In response to this evidence, Watson argues that there is not enough lipophilic substance in the inner volume of the granules to produce lipophilic characteristics. Watson relies on Dr. Park's testimony for support, who found that that the amount of magnesium stearate "is so small, you cannot exhibit lipophilic property based on such a small amount." (2016 Trial Tr. Day 2 at 157:17-21, Park Direct). However, Dr. Park did not cite any experiments or studies to confirm his opinion. Indeed, his opinion was contradicted by Shire's expert Dr. Sinko, who testified that "the primary issue is . . . the potency of the chemical." (2016 Trial Tr. Day 1 at 209:1-4, Sinko Direct). Dr. Sinko testified that it was well-known in the scientific literature that low levels of magnesium stearate could produce marked lipophilic effects. (*Id.* at 209:5-8, 209:12-211:24, 211:25-213:17, Sinko Direct; *see also id.* at 99:3-8, Little Cross (testifying that magnesium stearate "is one of the most lipophilic things I can imagine, so from a chemical structure standpoint, from how it resists penetration of water, it has been shown in .5 percent before to cause release inhibiting [e]ffects like that, resisting penetration of water . . ."). Additionally, such literature is consistent with the '720 Patent itself, which discloses granules containing only 2.4% lipophilic substances by weight. ('720 Patent, col. 5 ll. 30-45).

In a similar argument, Watson contends that the lipophilic or hydrophilic substance must constitute the "main component" of the respective lipophilic or hydrophilic matrix, and that "main component" should be understood quantitatively. (2016 Trial Tr. Day 1 at 42:21-23, Watson Opening; *see also* 2016 Trial Tr. Day 2 at 126:19-25, Park Direct). In support, Watson looks to a passage from the Federal Circuit citing the portion of the specification describing inert matrices where "the main component of the matrix structure" opposes some resistance to the

penetration of the solvent. *Watson II*, 787 F.3d at 1365-66 (citing '720 Patent, col. 1 ll.17-20). However, the Federal Circuit cited this passage to support its holding that the matrix exhibit lipophilic properties—not necessarily to support a holding that lipophilic substances must be present in a certain quantitative amount.

To the contrary, the Federal Circuit only held that the inner lipophilic matrix must exhibit lipophilic characteristics and be separate from the outer hydrophilic matrix. Defining the claims according to specific percentages of individual ingredients would contravene the Federal Circuit's emphasis on the characteristics of the matrices themselves, as opposed to the characteristics of the excipients. *See Watson II*, 787 F.3d at 1365-66 ("Thus, a 'lipophilic *matrix*' is more than just a matrix with at least one lipophilic *excipient*—the matrix itself must exhibit lipophilic characteristics.").

I find that magnesium stearate is the "main component" of the inner lipophilic matrix. According to both Drs. Sinko and Little, the "main component" is the structure responsible for the lipophilic or hydrophilic behavior. (2016 Trial Tr. Day 1 at 76:16-77:1, Little Direct; 2016 Trial Tr. Day 2 at 12:4-13, Sinko Cross). The quantity of a component alone is not a reliable indicator of the characteristics of the entire composition. (*See* 2016 Trial Tr. Day 2 at 12:9-13, Sinko Cross: "To say it quantitatively to me, I utterly disagree . . . I would say it has nothing to do strictly with quantity."). Both Dr. Sinkos and Little testified that some excipients, such as magnesium stearate, are "potent" in the sense that low quantities of individual components can lead to significant lipophilic characteristics. (2016 Trial Tr. Day 1 at 208:23-209:8, Sinko Direct; *id.* at 99:3-8, Little Cross). Thus, the "main component" of the inner lipophilic matrix—the magnesium stearate—exhibits the required lipophilic characteristics.

For the foregoing reasons, I find that the interior volume of the granules exhibits lipophilic characteristics and does not exhibit hydrophilic characteristics. This inner volume is separate from the outer volume. Accordingly, the Watson ANDA Product contains an inner lipophilic matrix—the volume within the granules—which exhibits lipophilic characteristics.

**d. Outer Hydrophilic Matrix Exhibits Hydrophilic Characteristics**

I must next determine whether the Watson ANDA Product also contains an outer hydrophilic matrix that exhibits hydrophilic characteristics. As described above, the specification describes "hydrophilic characteristics" such as "remarkably increase[d] viscosity inside the hydrated layer" or "a high viscosity swollen layer." ('720 Patent col.1 ll.21-26; *id.* at col.2 ll.60-64). Additionally, the Parties have stipulated that "hydrophilic" means "having an affinity to water." (2013 Order at 6). Here, the volume of the hydrophilic matrix—the extragranular space—displays the characteristics described by the '720 Patent. These characteristics are due to sodium starch glycolate's affinity towards aqueous fluids. (2016 Trial Tr. Day 1 at 75:12-77:7, 88:6-10, Little Direct; *id.* at 224:25-225:25, Sinko Direct).

Sodium starch glycolate has an affinity toward aqueous fluids and is recognized in the pharmaceutical industry as having dramatic swelling properties. (2016 Trial Tr. Day 2 at 172:22-173:6, Park Direct; *id.* at 224:16-22, 233:20-234:2, 245:8-17, Park Cross). Upon contact with aqueous fluids, sodium starch glycolate takes in water to swell, which further slows the penetration of the fluids into the composition. (2013 Order at 18 n.25; 2016 Trial Tr. Day 1 at 76:5-15, 77:18-78:13, 79:7-17, 81:3-83:14, Little Direct; *id.* at 225:20-25, 226:15-25, 227:23-228:19, Sinko Direct). In fact, sodium starch glycolate is known in the art as a "hydrogel," the class of hydrophilic compounds mentioned in the '720 Patent. (2016 Trial Tr. Day 2 at 191:8-16, 224:16-22, Park Cross).

The hydrophilic effect of sodium starch glycolate can be observed in the Watson ANDA tablet during dissolution. Based on Dr. Bugay's images, Dr. Sinko testified that the "vast majority" of sodium starch glycolate would exist outside of the granules, given its high molecular weight. (*Id* at 76:6-13, Sinko Redirect). In addition, Dr. Sinko testified that sodium starch glycolate occupied between 50-80% of the extragranular region. (*Id.* at 81:12-21).[13]

Dr. Little explained that during the first phases of dissolution, the Watson ANDA tablet swelled to the point that the coating was broken and eventually removed. (2016 Trial Tr. Day 1 at 81:3-82:9, Little Direct). Dr. Little observed a hydrated layer at 32 and 42 minutes that is indicative of the swelling that would be expected from a hydrophilic matrix of sodium starch glycolate. (*Id.* at 82:20-83:5). As the dissolution continued, the tablet's hydrated layer continued to swell, erode, disintegrate, and release granules—further evidence of a hydrophilic matrix. (*Id.* at 83:6-14, 83:23-84:7). Dr. Little testified at the 2013 Trial, and on remand, that this behavior—swelling upon contact with buffer, erosion of the hydrated layer, release of granular structures, and further disintegration of the hydrated layer—aligns with the '720 Patent's description of the behavior of the outer hydrophilic matrix. (2013 Trial Tr. Day 2 at 61:5-62:17, 63:5-12, Little Cross; 2016 Trial Tr. Day 1 at 75:12-76:15, 78:14-80:9, Little Direct).

For the foregoing reasons, I find that the extragranular volume exhibits hydrophilic characteristics and does not exhibit lipophilic characteristics. This outer volume is separate from the inner volume. Accordingly, the Watson ANDA Product contains an outer hydrophilic matrix—the extragranular volume—which exhibits hydrophilic characteristics.

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[13] For the reasons discussed above in reference to the inner lipophilic matrix, the sodium starch glycolate acts as the "main component" in the extragranular region.

**e. The Markush Groups**

Having found that Watson's ANDA Product contains an inner lipophilic and outer hydrophilic matrix, I find it necessary to address a particular argument made by Watson on remand. Watson contends that the Federal Circuit found that claim 1 excludes excipients from the inner volume of the granule (or, lipophilic matrix) that are not listed in the Markush group in claim 1(a), and that claim 1 similarly excludes excipients from the outer volume (or, hydrophilic matrix) that are not listed in in the Markush group in claim 1(b). Essentially, Watson contends that the Federal Circuit Opinion forecloses a finding of infringement when the volume of the inner lipophilic matrix contains one lipophilic substance and several hydrophilic substances. (2016 Trial Tr. Day 2 at 125:20-126:18, Park Direct; *see also* March 23, 2016 Closing Statement).

Watson presented this argument to the Federal Circuit, yet the Federal Circuit remanded the case—notwithstanding the presence of non-claim 1(a) excipients in the granule, and non-claim 1(b) excipients in the extragranular space.

The Federal Circuit's Mandate did not necessitate that hydrophilic excipients cannot be in the lipophilic matrix, or that lipophilic excipients cannot be in the hydrophilic matrix. The Federal Circuit's requirement is that the Markush group limitations compel a claim construction that requires that the inner lipophilic matrix is separate from, but does not necessarily require distinct excipients from, the outer hydrophilic matrix. *Watson II*, 787 F.3d at 1366. Indeed, the Federal Circuit contemplated that there could be situations where the matrices contain excipients outside of their respective Markush groups. *See* Watso*n II*, 787 F.3d 1359, 1368 ("Whether or not a composition infringes when there is a trace of hydrophilic molecules in the inner volume

because of the mixing step inherent in the manufacturing process, *for example*, is a question for the fact finder.") (emphasis added).

In terms of the composition of the granule, neither Shire nor Watson presented evidence as to the exact amount of magnesium stearate within the granule. Evidence was presented, however, that showed that within the inner volume of the granule, magnesium stearate could not exceed a theoretical maximum of 5%. (2016 Trial. Tr. Day 2 at 11:6-23, Sinko Cross). Additional evidence showed that the remaining excipients in the volume of the granule were hydrophilic substances. (*Id.* at 4-12, Sinko Cross). However, as discussed above, the magnesium stearate is the main component of the inner volume of the granules. The other hydrophilic excipients—including the sodium starch glycolate[14]—are unrelated to the function of the inner lipophilic matrix. (*See* 2016 Trial Tr. Day 1 at 70:1-4). The purpose of the inner lipophilic matrix is to contribute to the controlled release of the mesalamine. (2013 Order at p. 18, n.25). Drs. Sinko and Little reaffirmed at the 2016 Trial that the hydrophilic compounds in the granules do not affect the overall lipophilic character of that volume—they do not have an effect on the release of mesalamine from the granule. (2016 Trial Tr. Day 1 at 70:1-4).[15]

Watson contends that the purpose of the inclusion of magnesium stearate in the ANDA Product was as a lubricant. I previously found that magnesium stearate does act as a lubricant—however, I found that magnesium stearate only exhibited the characteristic of a lubricant when it

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[14] I previously found that sodium starch glycolate within the granules was irrelevant to the release of mesalamine in my 2013 Order. (2013 Order at 18, n. 25).

[15] Notably, in addition to the inner lipophilic and outer hydrophilic matrices provided in claim 1(a) and claim 1(b), claim 1(c) provides for "optionally other excipients." Neither of the Parties has briefed or argued about how I should construe claim 1(c). However, that claim 1 appears to allow "other excipients," tends to support that other excipients within the inner volume and outer volume, which are unrelated to the function of those volumes as inner lipophilic and outer hydrophilic matrices, would be permitted.

was in the extragranular space. (2013 Order at p. 18, n.25). I found that when magnesium stearate was located within the granule it affects the release of mesalmine. *Id.*

Additionally, Watson argues that the presence of magnesium stearate in the extragranular space means that the outer hydrophilic matrix (the extragranular volume) violates the claim 1(b) Markush group. However, the magnesium stearate in the extragranular space is overwhelmed by the hydrophilic properties of the sodium starch glycolate in the extragranular space. (2016 Trial Tr. Day 1 at 224:3-21, Sinko Direct (testifying that sodium starch glycolate is more "potent than the mag stearate outside")). The sodium starch glycolate is the main component of the extragranular volume, and I previously found that sodium starch glycolate in the extragranular space will affect the release of the mesalamine. (2013 Order at p. 18, n.25).

In short, the inner lipophilic matrix is comprised of the volume within the granules. The volume within the granules contains magnesium stearate, which falls within the claim 1(a) Markush group. The inner volume exhibits lipophilic characteristics. Other excipients, not within the claim 1(a) Markush group are present within the inner volume. However, these other excipients do not affect the lipophilic characteristic of the inner volume and, thus, are unrelated to the lipophilic matrix.

Similarly, the outer hydrophilic matrix is comprised of the volume outside of the granules, or, the extragranular space. The extragranular space contains sodium starch glycolate, which falls within the claim 1(b) Markush group. The extragranular space exhibits hydrophilic characteristics. Magnesium stearate, an excipient not within the claim 1(b) Markush group, is present within the extragranular space. However, the magnesium stearate does not affect the hydrophilic characteristic of the extragranular space and, thus, is unrelated to the hydrophilic matrix.

## V. Conclusion

Based upon my findings set forth above, and my undisturbed findings from the 2013 Order, Plaintiffs have established, by a preponderance of evidence, that the Watson ANDA Product meets the additional requirements established by the Federal Circuit for the claim constructions of "inner lipophilic matrix" and "outer hydrophilic matrix." Thus, Defendants have infringed claims 1 and 3 of the '720 Patent.

Additionally, as I found in the 2013 Order, Watson Pharmaceuticals, Inc. (now known as Actavis, Inc.) knowingly induced Watson Laboratories, Inc.—Florida, Watson Pharma, Inc., and/or Watson Laboratories, Inc. to infringe and/or contributed to Watson Laboratories, Inc.—Florida's, Watson Pharma, Inc.'s, and Watson Laboratories, Inc.'s infringement of '720 Patent, claims 1 and 3. (2013 Order at 30, n.42). Each of the Defendants induced or contributed to the construction of the Watson ANDA Product and the filing of ANDA No. 203817. *Id.*

Plaintiffs are, therefore, entitled to the requested injunctive relief. Final judgment shall issue by separate order.

**DONE AND ORDERED** in Chambers at West Palm Beach, this 25 day of March, 2016.

DONALD M. MIDDLEBROOKS
UNITED STATES DISTRICT JUDGE

Copies to: Counsel of Record

# THE UNITED STATES OF AMERICA

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November 29, 2012

THIS IS TO CERTIFY THAT ANNEXED HERETO IS A TRUE COPY FROM THE RECORDS OF THIS OFFICE OF:

U.S. PATENT: *6,773,720*
ISSUE DATE: *August 10, 2004*

By Authority of the
Under Secretary of Commerce for Intellectual Property
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R. PONDEXTER
Certifying Officer

PTX001
Shire v. Watson

US006773720B1

(12) **United States Patent**
**Villa et al.**

(10) **Patent No.: US 6,773,720 B1**
(45) **Date of Patent: Aug. 10, 2004**

(54) **MESALAZINE CONTROLLED RELEASE ORAL PHARMACEUTICAL COMPOSITIONS**

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( * ) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

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(57) **ABSTRACT**

Controlled-release oral pharmaceutical compositions containing as active ingredient 5-amino-salicylic acid, comprising: a) an inner lipophilic matrix consisting of substances with a melting point below 90° C. in which the active ingredient is at least partly inglobated; b) an outer hydrophilic matrix in which the lipophilic matrix is dispersed; c) optionally other excipients.

**4 Claims, No Drawings**

# MESALAZINE CONTROLLED RELEASE ORAL PHARMACEUTICAL COMPOSITIONS

The present invention relates to controlled release oral pharmaceutical compositions containing as active ingredient 5-amino salicylic acid, also named mesalazine.

## BACKGROUND OF THE INVENTION

Mesalazine is used in the treatment of Chron's disease and ulcerative colitis thanks to its antiinflammatory activity on the intestinal mucuses. Controlled-release formulations of mesalazine are disclosed in WO 95/16451, EP 0 453 001, EP 0 377 477.

The preparation of a sustained, controlled, delayed or anyhow modified release form can be carried out according to different known techniques:

1. The use of inert matrices, in which the main component of the matrix structure opposes some resistance to the penetration of the solvent due to the poor affinity towards aqueous fluids; such property being known as lipophilia.
2. The use of hydrophilic matrices, in which the main component of the matrix structure opposes high resistance to the progress of the solvent, in that the presence of strongly hydrophilic groups in its chains, mainly branched, remarkably increases viscosity inside the hydrated layer.
3. The use of biocrodible matrices, which are capable of being degraded by the enzymes of some biological compartment.

All the procedures listed above suffer, however, from drawbacks and imperfections.

Inert matrices, for example, generally entail non-linear, but esponential, release of the active ingredient.

Hydrophilic matrices have a linear behaviour until a certain fraction of active ingredient has been released, then they significantly deviate from linear release.

Bioerodible matrices are ideal to carry out the so-called "site-release", but they involve the problem of finding the suitable enzyme or reactive to degradation. Furthermore, they frequently release in situ metabolites that are not wholly toxicologically inert.

A number of formulations based on inert lipophilic matrices have been described: Drug Dev. Ind. Pharm. 13 (6), 1001–1022, (1987) discloses a process making use of varying amounts of colloidal silica as a porization element for a lipophilic inert matrix in which the active ingredient is incorporated.

The same notion of canalization of an inert matrix is described in U.S. Pat. No. 4,608,248 in which a small amount of a hydrophilic polymer is mixed with the substances forming an inert matrix, in a non sequential compenetration of different matrix materials.

EP 375,063 discloses a technique for the preparation of multiparticulate granules for the controlled-release of the active ingredient which comprises co-dissolution of polymers or suitable substances to form a inert matrix with the active ingredient and the subsequent deposition of said solution on an inert carrier which acts as the core of the device. Alternatively, the inert carrier is kneaded with the solution containing the inert polymer and the active ingredient, then the organic solvent used for the their dissolution is evaporated off to obtain a solid residue. The resulting structure is a "reservoir", i.e. is not macroscopically homogeneous along all the symmetry axis of the final form.

The same "reservoir" structure is also described in Chem. Pharm. Bull. 46 (3), 531–533, (1998) which improves the



application through an annealing technique of the inert polymer layer which is deposited on the surface of the pellets.

To the "reservoir" structure also belong the products obtained according to the technique described in WO 93/00889 which discloses a process for the preparation of pellets in hydrophilic matrix which comprises:

- dissolution of the active ingredient with gastro-resistant hydrophilic polymers in organic solvents;
- drying of said suspension;
- subsequent kneading and formulation of the pellets in a hydrophilic or lipophilic matrix without distinction of effectiveness between the two types of application.

EP 0 453 001 discloses a multiparticulate with "reservoir" structure inserted in a hydrophilic matrix. The basic multiparticulate utilizes two coating membranes to decrease the release rate of the active ingredient, a pH-dependent membrane with the purpose of gastric protection and a pH-independent methacrylic membrane with the purpose of slowing down the penetration of the aqueous fluid.

WO 95/16451 discloses a composition only formed by a hydrophilic matrix coated with a gastro-resistant film for controlling the dissolution rate of mesalazine.

When preparing sustained-, controlled-release dosage forms of a medicament topically active in the gastrointestinal tract, it is important to ensure a controlled release from the first phases following administration, i.e. when the inert matrices have the maximum release rate inside the logarithmic phase, namely the higher deviation from linear release.

Said object has been attained by the present invention, which also allows to prepare compositions characterized by a high content in active ingredient.

## DISCLOSURE OF THE INVENTION

The invention provides controlled release oral pharmaceutical compositions containing 5-amino-salicylic acid as the active ingredient, comprising:

a) an inner lipophilic matrix consisting of substances with melting point below 90° C. in which the active ingredient is at least partially inglobated;
b) an outer hydrophilic matrix in which the lipophilic matrix is dispersed;
c) optionally other excipients.

## DETAILED DISCLOSE OF THE INVENTION

The compositions of the invention can be obtained with a method comprising the following steps:

a) the active ingredient is first inglobated in a low melting excipient or mixture of excipients, while heating to soften and/or melt the excipient itself, which thereby incorporates the active ingredient by simple dispersion.

After cooling at room temperature an inert matrix forms, which can be reduced in size to obtain matrix granules containing the active ingredient particles.

b) the inert matrix granules are subsequently mixed together with one or more hydrophilic water-swellable excipients.

This way, when the tablet is contacted with biological fluids, a high viscosity swollen layer is formed, which coordinates the solvent molecules and acts as a barrier to penetration of the aqueous fluid itself inside the new structure. Said barrier antagonizes the starting "burst effect" caused by the dissolution of the medicament inglobated inside the inert matrix, which is in its turn inside the hydrophilic matrix.

The lipophilic matrix consists of substances selected from unsaturated and/or hydrogenated fatty acids, salts, esters or amides thereof, fatty acids mono-, di- or triglycerids, waxes, ceramides, cholesterol derivatives or mixtures thereof having melting point within the range of 40 to 90° C.

If desired, a fatty acid calcium salt may be incorporated. in the lipophilic matrix which is subsequently dispersed in a hydrophilic matrix prepared with alginic acid, thus remarkably increasing the hydrophilic matrix viscosity following penetration of the solvent front until contact with the lipophilic matrix granules dispersed inside.

The weight content of the active ingredient in the lipophilic matrix usually ranges from 5 to 95%.

The inert lipophilic matrix is reduced into granules by an extrusion and/or granulation process, or any other known processes which retain the homogeneous dispersion and matrix structure of the starting mixture.

The hydrophilic matrix consists of excipients known as hydrogels, i.e. substances which pass from the dry state to the hydrated one, undergo the so-called "molecular relaxation", namely a remarkable increase in mass and weight following the coordination of a large number of water molecules by the polar groups present in the polymeric chains of the excipients themselves.

Examples of hydrogels which can be used according to the invention are compounds selected from polymers or copolymers of acrylic or methacrylic acid, alkylvinyl polymers, hydroxyalkyl celluloses, carboxyalkyl celluloses, polysaccharides, dextrins, pectins, starches and derivatives, natural or synthetic gums, alginic acid.

The lipophilic matrix granules containing the active ingredient are mixed the with hydrophilic compounds cited above in a weight ratio typically ranging from 100:0.5 to 100:20 (lipophilic matrix: hydrophilic matrix). Part of mesalazine can optionally be mixed with hydrophilic substances to provide compositions in which the active ingredient is dispersed both in the lipophilic and the hydrophilic matrix, said comoositions being preferably in the form of tablets, capsules and/or minitablets.

The compression of the mixture of lipophilic matrix, hydrogel-forming compounds and, optionally, active ingredient non inglobated in the lipophilic matrix, yields a macroscopically homogeneous structure in all its volume, namely a matrix containing a dispersion of the lipophilic granules in a hydrophilic matrix.

The tablets, capsules and/or minitablets obtainable according to the invention can optionally be subjected to known coating processes with a gastro-resistant film, consisting of for example polymers of methacrylic acids (Eudragit$^{(R)}$) or cellulose derivatives, such as cellulose acetophthalate.

The compositions of the invention can contain a high percentage of active ingredient compared with the total composition weight up to 95%, an advantageous characteristic in the case of mesalazine which requires rather high unitary doses.

In terms of dissolution characteristics, the compositions of the invention provide a release profile of the active ingredient more homogeneous than the traditional systems. In fact, the immediate penetration of water inside the superficial layer of the hydrophilic matrix and the consequent swelling due to the distension of the polymeric chains of the hydrogels, gives rise to a high viscosity hydrated front which prevents the further penetration of water, linearly slowing down the dissolution process to a well determined point which can be located at about half the thickness until the further penetration of water would cause the disintegration



of the hydrophilic layer and therefore the release of the content which, consisting of lipophilic granules, however induces the diffusional mechanism typical of these structures and therefore further slows down the dissolution profile of the active ingredient.

The following examples illustrate the invention in greater detail.

EXAMPLE 1

770 g of 5-aminosalicylic acid are added in a kneader with 20 g of carnauba wax and 50 g of stearic acid with heating until homogeneous dispersion, then extruded into small granules while cold.

The inert matrix granules are loaded into a mixer in which 30 g of Carbopol 971P$^{(R)}$ and 65 g of hydroxypropyl methylcellulose are sequentially added.

After a first mixing step for homogeneously dispersing the powders, 60 g of microcrystalline cellulose and 5 g of magnesium stearate are added. After mixing, the final mixture is tabletted to unitary weight of 649 mg/tablet or 510 mg/tablet to obtain 500 and 400 mg dosages, respectively.

The resulting tablets are film-coated with cellulose acetophthalate or polymethacrylates and a plasticizer to provide gastric resistance and prevent the early release of product in the stomach.

The dissolution profile of these tablets shows the release of an active ingredient amount lower than 30% within the first hour of permanence in simulated enteric juice, an amount lower than 60% at the fourth hour and an amount lower than 90% at the eighth hour, thus proving that the double matrix effectively controls dissolution.

EXAMPLE 2

1000 g of 5-aminosalicylic acid are added in a kneader with 10 g of carnauba wax and 20 g of stearic acid with heating until homogeneous dispersion, then extruded into small granules while cold or directly granulated in a high rate mixer.

The resulting granules are loaded into a mixer in which 80 g of hydroxypropyl methylcellulose and 12 g of sodium starch glycolate are sequentially added. After a first mixing step, 11 g of silica colloidal and 11 g of magnesium stearate are added. The final mixture is homogenized, then tabletted to a unitary weight of 1144 mg/tablet.

The resulting tablets are then film coated with polymethacrylates or cellulose acetophthalate and plasticizers to provide gastric resistance.

The dissolution profile of these tablets after a lag time of permanence in the stomach and partly in the intestine provides the release of no more than 30% within the first hour, no more than 55% within two hours, no more than 70% within four hours, no more than 90% within eight hours.

EXAMPLE 3

850 g of 5-aminosalicylic acid are added in granulator/kneader with 9 g of beeswax and 22 g of palmitic acid with heating, until homogeneous dispersion; then worked to a granulate in a high shear granulating device. The resulting granules are then loaded into a mixer which is added in succession with 45.5 g of hydroxypropyl methylcellulose, 45.5 g of microcrystalline cellulose, 20 g of sodium starch glycolate, 22 g of colloidal silica and 22 g of magnesium stearate. After homogenization, the final mixture is tabletted to a unitary weight of 975 mg/tablet.

The resulting tablets are then film coated with polymethacrylates or acetophthalate of cellulose and plasticizers to provide gastric resistance.

The dissolution profile of these tablets after a lag time of permanence in the stomach and partly in the intestine provides the release of no more than 30% within the first hour, no more than 50% within two hours, no more than 70% within four hours, no more than 90% within eight hours.

EXAMPLE 4

1100 g of 5-aminosalicylic acid are added in granulator/kneader with 10 g of wax carnauba and 20 g of stearic acid.

10 g of polyacrylamide, 39.5 of microcrystalline cellulose and 22 g of colloidal silica are separately loaded into the homogenizer/granulator to obtain a homogeneous solid mixture, which is placed in the mixer where the active ingredient has been granulated and homogenized. 49.5 g of hydroxypropyl methylcellulose and 12 g of sodium alginate are thoroughly mixed, then added with 5 g of calcium carbonate, 34.5 g of microcrystalline cellulose and 11 g of magnesium stearate. The mixture is homogenized, then tabletted to a final unitary weight of 1194 mg/tablet. The resulting tablets are then film-coated with polymethacrylates or cellulose acetophthalate and plasticizers to provide gastric resistance.

The dissolution profile of these tablets after a lag time of permanence in the stomach and partly in the intestine provides the release of no more than 35% within the first hour, no more than 50% within two hours, no more than 70% within four hours, no more than 90% within eight hours.

EXAMPLE 5

1200 g of 5-aminosalicylic acid are added in mixer with 10 g of carnauba wax and 20 g of stearic acid, with heating until homogeneous dispersion, then cold extruded into small granules or directly granulated in the high rate mixer. The resulting granules are loaded into a mixer, then 70 g of hydroxypropyl methylcellulose and 20 g of sodium starch glycolate are sequentially added.

After a first mixing step, 80 g of sodium carbonate and 5 g of magnesium stearate are added. The final mixture is homogenized, then tabletted to unitary weight of 1375 mg/tablet.

The resulting tablets are then film-coated with polymethacrylates or cellulose acetophthalate and plasticizers to provide gastric resistance.



The dissolution profile of these tablets after a lag time of permanence in the stomach and partly in the intestine provides the release of no more than 30% within the first hour, no more than 50% within two hours, no more than 70% within four hours, no more than 90% within eight hours.

What is claimed is:

1. Controlled-release oral pharmaceutical compositions containing as an active ingredient 5-amino-salicylic acid, comprising:

a) an inner lipophilic matrix consisting of substances selected from the group consisting of unsaturated and/or hydrogenated fatty acid, salts, esters or amides thereof, fatty acid mono-, di- or triglycerids, waxes, ceramides, and cholesterol derivatives with melting points below 90° C., and wherein the active ingredient is dispersed both in said the lipophilic matrix and in the hydrophilic matrix;

b) an outer hydrophilic matrix wherein the lipophilic matrix is dispersed, and said outer hydrophilic matrix consists of compounds selected from the group consisting of polymers or copolymers of acrylic or methacrylic acid, alkylvinyl polymers, hydroxyalkyl celluloses, carboxyalkyl celluloses, polysaccharides, dextrins, pectins, starches and derivatives, alginic acid, and natural or synthetic gums;

c) optionally other excipients;

wherein the active ingredient is present in an amount of 80 to 95% by weight of the total composition, and wherein the active ingredient is dispersed both in the lipophilic matrix and in the hydrophilic matrix.

2. Compositions as claimed in claim 1, wherein 5-aminosalicylic acid is dispersed in a molten lipophilic matrix by kneading, extrusion and/or granulation.

3. Compositions as claimed in claim 1, in the form of tablets, capsules, mintablets.

4. A process for the preparation of the compositions of claim 1, which comprises:

a) melt granulation of at least one portion of the active ingredient with the lipophilic excipients with melting point lower than 90° C.;

b) mixing the granules from step a) with the hydrophilic excipients and subsequent tabletting or compression.

* * * * *

## PROOF OF SERVICE

I hereby certify that on May 4, 2016, one copy of the foregoing **BRIEF OF DEFENDANTS-APPELLANTS WATSON PHARMACEUTICALS, INC. (now known as Actavis, Inc.), WATSON LABORATORIES, INC. – FLORIDA (now known as Actavis Laboratories FL, Inc., WATSON PHARMA, INC. (now known as Actavis Pharma, Inc.), and WATSON LABORATORIES, INC.** was filed electronically using the CM/ECF system, which will send notification of such filing to counsel of record for Plaintiffs-Appellees.

Dated: May 4, 2016

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**CERTIFICATE OF COMPLIANCE**
**WITH TYPE-VOLUME LIMITATION, TYPEFACE REQUIREMENTS, AND TYPE STYLE REQUIREMENTS**

Counsel for Defendants-Appellants Watson Pharmaceuticals, Inc., Watson Laboratories, Inc. – Florida, Watson Pharma, Inc., and Watson Laboratories, Inc. certifies the following:

1. This brief complies with the type-volume limitation of Federal Rule of Appellate Procedure 32(a)(7)(B)

The brief contains 13,539 words, excluding the parts of the brief exempted by Federal Rule of Appellate Procedure 32(a)(7)(B)(iii) and Federal Circuit Rule 32(b).

2. This brief complies with the typeface requirements of Federal Rule of Appellate Procedure 32(a)(5) and the type style requirements of Federal Rule of Appellate Procedure 32(a)(6).

This brief has been prepared in a proportionally spaced typeface using Microsoft Word 2013 in 14-point New Times Roman font.

Respectfully submitted,

**MADDOX EDWARDS, PLLC**

Dated: May 4, 2016

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